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THE PATHOGENESIS OF BRONCHIECTASIS*

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BOSTON

SINCE Laennec[1] first described and named bronchiectasis its etiology and mode of development have been controversial issues. Numerous theories have been advanced, each of which is backed by voluminous evidence, but no one of which satisfactorily explains all types or features of the disease. Either the underlying cause remains undiscovered or multiple factors exist that predispose to or result in dilatation of portions of the bronchial tree. I propose, in the short time at my disposal, to review briefly the more significant of these possible factors and to compare their relative importance and interrelation.

Four important clinical and anatomic features of the disease must be explained by any theory of pathogenesis that can be considered satisfactory. First, bronchiectasis is rarely a diffuse disease of the bronchial tree. It characteristically involves a group of adjoining bronchi such as those of a lobe or a portion of a lobe — for example, the lingula of the left upper lobe. The affected segments of the tree may be, and frequently are, multiple but bronchi in the uninvolved areas are entirely normal.

Secondly, bronchiectasis is not usually a progressive disease. Most cases come under observation with well developed segmental involvement, and over months or years no extension to other portions of the bronchial system will be apparent unless an attack of pneumonia supervenes, when another segment may become involved.

Thirdly, bronchiectasis is rarely seen as an isolated finding in an otherwise normal lung. The surrounding pulmonary parenchyma is characteristically although variably abnormal. In the earlier literature, based primarily on post-mortem studies, acute and chronic pneumonitis was usually recorded, and Lord[2] was so impressed with parenchymal involvement that he preferred the term "bronchopulmonary sepsis" to bronchiectasis. In the present era, when lobectomy specimens are available from which to study earlier stages of the disease, septic pneumonitis is unusual, but the surrounding lung is rarely normal. The changes vary widely from case to case, however, and may comprise atelectasis, fibrosis, organized pneumonitis, focal emphysema or even total destruction of alveolar tissue.

Fourthly, although bronchiectasis can develop at any age, it is characteristically a disease of youth. Onset in the first decade was recorded in 42 per cent of Perry and King's[3] series, and 69 per cent of their patients developed the disease before twenty years of age. With these four points in mind, the various theories of pathogenesis will be considered.

CHRONIC BRONCHIAL INFECTION

Bronchiectasis is ordinarily associated with a chronic productive cough, and the sputum is characteristically abundant and purulent. In the days before modern contrast radiography with lipiodol instillation the evidence of bronchitis frequently preceded by long intervals the physical signs or x-ray appearance that would permit the diagnosis of bronchiectasis. Moreover, in autopsy or even resected specimens, evidence of chronic infection of the bronchial walls was almost uniformly present. The assumption that bronchial infection was primary and induced bronchial dilatation by injury to the skeletal structures of the bronchial walls, the musculoelastic tissues and the cartilaginous rings was not unreasonable. The chronic cough was thought by some to have a dilating effect on the bronchi, despite the fact, as Andrus[4] points out, that during cough the pressure is greater in the alveoli than in the bronchi, which therefore tend to be compressed rather than dilated. The deep inspiration preceding cough has, it is true, a bronchodilating effect but is of such brief duration that its effect is probably unimportant. The pressure of stagnant secretions was proposed by Laennec[5] himself as a dilating agent, but of course cannot be a factor in the "dry" types of bronchiectasis in which no secretion is present over long periods.

If ordinary bronchitis were a frequent cause of bronchiectasis one would expect the disease to be,

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like emphysema, a geriatric rather than a pediatric problem. Many efforts have consequently been made to isolate specific organisms of exceptional virulence or of peculiar histolytic properties that would explain the extensive destruction of bronchial walls. Such attempts have been entirely unsuccessful.[6] The organisms found in bronchiectatic secretions are variable, numerous and usually mixed. Staphylococci, streptococci of numerous types and *Haemophilus influenzae* are usually present, spirochetes and fusiform bacilli are sometimes seen, and a wide variety of other organisms may be found from case to case and even from time to time in the same patient. Entirely similar flora may be observed in bronchitis without bronchial dilatation.

Careful pathological studies by Robinson[7, 8] of the affected bronchial walls in a series of lobectomy specimens showed the constant presence of severe inflammatory infiltration. Frequently, these infiltrates surrounded or invaded the scanty remnants of the musculoelastic tissues and the cartilaginous rings. These pictures were interpreted as evidence of active destruction of these elements by the inflammatory process. In a survey of lobectomy specimens I found severe bronchial inflammation of the type described by Robinson in 35 of 50 cases. In the remainder the inflammation was comparatively mild and in a case of so-called "dry bronchiectasis" was entirely absent. There was no close parallelism between the severity of inflammation and the degree of bronchial dilatation. Moreover, in a series of lungs from patients who had suffered from chronic asthma, in which no dilatation of bronchi was present and in which inflammatory infiltration sometimes exceeded that found in frank bronchiectasis, active necrotizing bronchitis was observed in only 3 cases. Its absence at the time of lobectomy does not, of course, deny the possibility of its existence in the past. When allowance is made for the stretching and atrophic effects of chronic dilatation it is doubtful if the evidence for active destruction of bronchial structures is adequate in most cases.

Congenital Abnormalities

The most important of the congenital abnormalities is the condition termed "congenital cystic disease." Outgrowths or buds of bronchial tissues from the trachea and major bronchi into the tissues of the mediastinum are not infrequent. These may produce cysts lined with ciliated or pseudostratified epithelium and may contain in their walls varying amounts of muscle, cartilage and glandular tissue. If the lumen of the stalk is obliterated they become distended with mucinous fluid.

That similar bronchial outgrowths that fail to differentiate into alveolar tissue may develop within the lung itself is not improbable, and lung cysts with or without connection with the lumen of bronchi have frequently been described.[9–11] The criteria for their recognition, however, are far from adequate, and nearly all the features considered characteristic of congenital cystic disease are seen from time to time in bronchiectases that are almost certainly acquired. The existence of congenital cystic disease cannot be denied, but it seems probable that the diagnosis has been made far too frequently and with insufficient realization of how early in infancy and childhood acquired bronchiectasis may develop.

An indirect result of congenital influence is clearly shown by the cases of situs inversus with bronchiectasis of the lower lobe and coincident sinusitis.[12] The contention of Sauerbruch[13] that many patients destined to develop bronchiectasis have inherited bronchial defects is difficult to disprove but lacks positive supporting evidence.

Bronchostenosis

Stenosis of major bronchi is frequently associated with progressive ectasia of the subtending divisions. Aspirated foreign bodies, intrabronchial tumors such as adenomas and slowly growing carcinomas, bronchial cicatrices due to syphilis or tuberculosis and peribronchial pressure from enlarged hilar lymph nodes, such as the primary complex of tuberculosis, have frequently been reported as initiating factors in the development of bronchiectasis.[14] Their influence cannot be denied, but the assumption of a direct causal relation is not necessarily valid. Fleischner,[14] in an interesting paper, reports 3 examples of bronchostenosis, the first associated with emphysema but no bronchial dilatation, the second with moderate ectasia but abundant purulent sputum and the third with extreme bronchial dilatation but no evidence of inflammation. Eloesser,[15] in a very thoughtful discussion of bronchostenosis, emphasizes the importance of Conner's[16] review of tracheobronchial syphilis. Although obstruction was present in nearly all cases only 15 per cent showed bronchial dilatation, and in 2 cases the bronchiectasis was limited to a portion of a lobe even though the stenosis was in the primary bronchus.

Another important group of cases to be considered in relation to the effects of bronchostenosis consists of the chronic asthmatic patients. In these patients functional narrowing of the bronchi exists over many years. In a group of 60 such cases that I have personally studied bronchiectasis was so exceptional that it appeared coincidental, although emphysema and cor pulmonale were of common occurrence.

Stenosis of bronchi, therefore, evidently does not regularly induce dilatation of the distal branches. If the obstruction is incomplete and expiration is impeded more than inspiration the alveoli rather than the bronchi tend to dilate, and emphysema results. With complete obstruction atelectasis follows, and this, as demonstrated below, is an important factor in the development of bronchial dilatation. Bronchostenosis, like obstruction in other duct

systems of the body, is also an important factor in the development and chronicity of infections, and infection of bronchi and of pulmonary parenchyma is another significant factor in the development of bronchiectasis. Finally, although a contributory role cannot be denied to bronchostenosis in many cases, the great majority of bronchiectatic lungs show no evidence whatever of narrowing of the bronchial tree proximal to the areas of dilatation.

Atelectasis

To the radiologists and the pediatricians we owe a group of very important studies linking the development of bronchiectasis with persistent atelectasis.[17–20] Anspach[17] in particular has called attention to the frequency in infancy and childhood of a triangular shadow at the base of the lung field due to persistent atelectasis of a lower lobe or a large segment of such a lobe. Bronchograms following lipiodol injection regularly show dilatation of bronchi throughout this atelectatic area. In cases in which bronchoscopic drainage or other appropriate treatment is successful in relieving the atelectasis the bronchi may revert to normal. More frequently, however, the ectasia is already irreversible when first observed. Similar observations of reversible bronchial dilatation associated with atelectasis have been described by Singer and Graham[21] under the term "pseudobronchiectasis."

The mechanism by which atelectasis induces bronchial dilatation has been discussed in detail by Andrus[4] and others.[20, 22] With collapse or destruction of huge amounts of pulmonary parenchyma a potential space is created within the pleural cavity, and the negative intrapleural pressure increases from a normal of −4 to −6 mm. to figures as great as −30 to −40 mm. Numerous compensatory factors are brought into play. The chest wall is relatively rigid, but the diaphragm rises, the mediastinum shifts toward the affected side, and the neighboring pulmonary tissue overexpands. Despite these adjustments the intrapleural pressure remains more negative than normal, and this negative pressure is transmitted through the solid nonexpanded pulmonary tissue to the elastic and expansible bronchial walls. Here at last one finds an effective dilating force, which is constant for the duration of the atelectasis.

It must be emphasized that it is not atelectasis per se that tends to dilate bronchi but the effect of the exaggerated negative intrathoracic pressure. In therapeutic pulmonary collapse, when air is periodically introduced into the pleural cavity and negative pressures do not develop, pulmonary atelectasis may be maintained for long periods without danger of bronchial dilatation.

Strong opponents of the theory that atelectasis induces bronchiectasis are Tannenberg and Pinner.[23] In carefully carried out experiments in rabbits atelectasis was produced by several means. Bronchiectasis did not develop unless the bronchi were simultaneously infected. It is by no means certain, however, that experiments on a small quadruped can fairly be used in drawing conclusions regarding man.

Pneumonia and Other Forms of Pneumonitis

In all reports of series of bronchiectatic cases histories of pneumonia or of upper respiratory infections frequently complicated by pneumonia, such as measles, pertussis and influenza have been obtained in 50 per cent or more of the patients (Ballon, Singer and Graham,[24] Perry and King[3] and Ogilvie[22]). Unfortunately, the nature of the pneumonic process can rarely be established from the available data. It is certainly unusual to see a typical pneumococcal pneumonia progress to bronchiectasis. In contrast, Opie and his associates[25] described the development of acute bronchiectasis following the 1918 influenza epidemic, and Kay[26] has recently reported 20 cases that were the sequel to atypical pneumonia in World War II. A significant number of patients trace the onset of their disease to a tonsillectomy, and another group to aspiration of foreign bodies — both common causes of septic pneumonitis. In autopsy and in resected specimens extensive inflammation of the pulmonary parenchyma is frequently observed, or patches of fibrosis may permit one to infer its presence in the past. In many cases, however, there is nothing to suggest the possibility of antecedent pneumonitis.

Discussion

Five factors — direct bronchial infection, congenital malformation of the bronchial tree, bronchial stenosis, pulmonary atelectasis and pneumonitis, with its sequel, pulmonary fibrosis, — have been discussed in relation to the pathogenesis of bronchiectasis. It has been shown that there is positive evidence to indicate a causal relation in certain cases for each of the five but that no one of them is constant or can explain all cases. The complexity of the situation is shown by Tables 1 and 2, which were prepared from a survey of fifty unselected lobectomy specimens. No case considered to be of congenital origin appeared in the series, and bronchostenosis was present in only 3 cases.

Table 1. *Factors Present in 50 Cases of Bronchiectasis.*

Factor	Total Cases	Severe Grade	Solitary Occurrence
Bronchitis	49	35	0
Atelectasis	43	24	0
Pneumonitis	43	19	0
Fibrosis	40	17	0
Bronchostenosis	3	3	0
Emphysema	6	0	1

It is evident from Table 1 that bronchial inflammation, atelectasis, active pneumonitis and fibrosis

were each present in 80 or more per cent of the specimens but that no one of these factors was constant and no one of them was ever a solitary finding unassociated with at least one other of the group. The combinations varied as is shown in Table 2.

It may safely be concluded that acquired bronchiectasis is generally a disease of the pulmonary parenchyma, as well as of the bronchial tree itself. This parenchymal involvement varies in detail, but one feature is common to all varieties: a noteworthy reduction in the number of aerated alveoli, potentially reversible in cases of atelectasis or early pneumonitis and certainly irreversible in cases of pulmonary fibrosis. Such a reduction in aerated parenchyma lowers the intrathoracic pressure and thereby generates an effective dilating force on the bronchial walls. The lack of aerated alveoli behind the involved bronchi renders cough ineffective as a mechanism for clearing bronchial secretions, since no current of air is generated, and stagnation of secretions becomes inevitable in dependent bronchi.

The assumption of primary bronchitis and secondary atelectasis with or without pneumonitis meets the test of the four criteria proposed above. Bronchial infection may cause atelectasis by obstructing the aeration of the alveoli with mucopurulent secretions. Infants and children are particularly prone to such obstructive atelectasis because the collateral air circulation through the pores of Kohn does not develop until adult life. They are also susceptible to pulmonary infections, in which bronchitis and atelectasis are more frequent than true pneumonic consolidation. Atelectasis is most likely to develop in the lower or middle lobes and in the lingula of the left upper lobe — the same distribution in which bronchiectasis is most usual. The most hopeful prophylactic measure in the prevention of bronchiectasis is therefore the prevention or prompt alleviation of atelectasis.

TABLE 2. *Pulmonary Parenchyma in Bronchiectasis.*

COMBINATION	NO OF CASES
Bronchitis, atelectasis, pneumonitis, fibrosis and emphysema	3
Bronchitis, atelectasis, pneumonitis and fibrosis	33
Bronchitis, atelectasis and pneumonitis	5
Bronchitis, atelectasis and fibrosis	2
Bronchitis, pneumonitis and fibrosis	3
Bronchitis and atelectasis	2
Bronchitis and pneumonitis	2
Bronchitis and fibrosis	1
Bronchitis and emphysema	1
Emphysema	1

SUMMARY

Five factors — chronic bronchial infection, congenital abnormalities of the bronchial tree, bronchostenosis, pulmonary atelectasis and pneumonitis or its sequel, pulmonary fibrosis — have been shown to be potential factors in the etiology of bronchiectasis. Of these, congenital cystic disease and bronchostenosis are comparatively uncommon. Bronchial inflammation alone is rarely an effective factor but in combination with atelectasis or pneumonitis adequately accounts for most of the characteristic features of the disease.

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AMEBIASIS

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NOW that World War II is over, it will be well to remember that a large part of the armed forces have seen service in areas heavily infected with *Endamoeba histolytica*. Most of these men and women have returned to their homes in the United States. A certain portion of them will have become infected with *E. histolytica*. The long incubation period of amebiasis, the comparatively mild nature of its symptomatology in many cases, the long period of symptom-free remissions and its tendency to recur merely emphasize the necessity that its presence be recognized. It is essential to realize not only that this disease may occur in returning veterans but also that cross-infection occurs in temperate zones and that the symptomless carrier, as well as the mild unrecognized case, serves as a reservoir of infection of the civilian population.

In the northeastern states amebiasis has always been endemic. Although several surveys of sample populations by the method of stool examination indicate that from 5 to 10 per cent of the people at some time harbor *E. histolytica* in their intestines, Faust[1] expressed the belief that an average incidence as high as 20 per cent, rather than the accepted figure of 5 to 10 per cent, may be reached in the United States. Table 1 presents the cases of amebic dysentery observed in Massachusetts from 1935 through 1945.[2] In 1944 and 1945 all cases but 1 were reported from the Army medical installations stationed in Massachusetts. In the years 1938–1939 Maine and New Hampshire reported only 1 case of amebiasis each. New York, in the same years, reported 153 cases. In 1937 Brenner[3] described 15 cases of amebiasis seen at the Peter Bent Brigham Hospital. In these cases one third of the patients had contracted the infection in New England.

That amebiasis is prevalent in the temperate zones and is not a disease limited to the tropical areas has repeatedly been emphasized. Judging by the paucity of reported cases in New England, one is led to believe either that the disease is not being recognized or that it is not being reported. It is our opinion that both beliefs are probably true. In any event, the war has created a much greater reservoir of people infected with *E. histolytica* who live in temperate zones. It is therefore considered timely to stress some of the clinical aspects of cases studied that are of value in the diagnosis of this disease. The clinical aspects of 60 cases of amebiasis seen in the Lovell General Hospital from January, 1945, to June, 1946, are presented below. The patients have been discharged from the Army and reside in the following states: Massachusetts (32 patients), Connecticut (12 patients), New York (7 patients), Maine (4 patients), Rhode Island (3 patients) and New Hampshire (2 patients).

The duration of symptoms varied from a few days to eleven years, one patient having had symptoms referable to the colon that had been present for the latter period of time. This case had previously been diagnosed as an "irritable colon." It was of interest that the symptoms occurred after a visit to the World's Fair in Chicago in 1933. There is some question, however, whether the symptoms were entirely due to amebic infestation, for in the last month they had become more marked. It was only at that time that stool examinations were done and cysts of *E. histolytica* found. There was a complete remission of symptoms following a course of Diodoquin. It would have required a longer period of observation, which was not possible in this case, to ascertain whether the symptomatology was entirely due to infection with *E. histolytica* or whether there was some underlying psychogenic disturbance. Symptoms were present for periods of less than three months in 12 cases and from three months to one year in 29. In 18 cases, symptoms were present for longer than one year.

The most frequent symptom was diarrhea (Table 2). In 25 cases the diarrhea was bloody. This varied from frankly bloody to merely blood-streaked stools. In a few cases there was rectal bleeding following defecation simulating that frequently seen in bleeding hemorrhoids. In 27 cases the stools were nonbloody; they were generally watery and brown. A fairly large percentage of these stools contained variable amounts of mucus. The severity of the diarrhea differed considerably. The number of stools varied from one to twenty a day. The patients often stated that the stools were normal between attacks of diarrhea. On close questioning, however, it was found that the stools were not of the same consistence as those prior to the onset of the diarrhea, but were somewhat loose and mushy.

The next most frequent symptom was abdominal pain. The pain was generally mild although in a few cases it was rather severe. In most cases it was low abdominal or periumbilical. It was generally described as crampy and was often relieved by defecation. In a few cases the pain was epigastric and closely simulated that of a peptic ulcer. In only 1 case was abdominal pain present without an associated diarrhea. In 7 cases there was a

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history of right-upper-quadrant pain. All these patients had liver involvement and are discussed in detail below. We have not included under abdominal pain 5 patients who complained of epigastric distress but have listed that symptom separately.

Loss of weight was a prominent symptom, occurring in 11 cases. The weight loss varied from 10 to 40 pounds. In these cases, 5 patients had amebic hepatitis, and 1 had amebic liver abscess. The remainder had no involvement of the liver. Six patients with and only 5 of the 53 without liver involvement showed weight loss. In the latter group, 2 patients had concomitant recurrent malaria, which also probably played a part in the weight loss. Nausea, anorexia and vomiting were the next most prominent symptoms. Nausea and vomiting occurred only in association with either diarrhea or abdominal pain. Less frequent symptoms were fatigability, dyspepsia, feverishness and chills. The last two were present only in patients with liver involvement. In 3 cases constipation was the only change in bowel habit and was not associated with diarrhea. Chest pain, joint swelling and hemoptysis occurred as the presenting symptoms in 1 patient with amebic liver abscess and bronchohepatic fistula. In 2 cases the patients complained of alternating diarrhea and constipation.

TABLE 1. *Cases of Amebic Dysentery Reported from Army Installations, Civilian Hospitals and Private Physicians in Massachusetts.*

YEAR	TOTAL CASES	CASES REPORTED FROM ARMY INSTALLATIONS	CASES REPORTED BY PRIVATE PHYSICIANS AND CIVILIAN HOSPITALS
1935	12	0	12
1936	3	0	3
1937	3	0	3
1938	1	0	1
1939	3	0	3
1940	4	0	4
1941	4	0	4
1942	3	0	3
1943	1	0	1
1944	2	2	0
1945	18	17	1*

*Retired veteran.

TABLE 2. *Symptomatology in Amebiasis.*

SYMPTOM		NO. OF CASES
Diarrhea		52
Nonbloody	27	
Bloody	25	
Abdominal pain		38
Nausea		11
Weight loss		11
Anorexia		9
Fatigue		6
Vomiting		6
Dyspepsia		5
Epigastric distress		5
Chills and fever		6
Constipation		3
Alternating diarrhea and constipation		2
Pain in rectum and coccyx		2
Joint swellings		1
Hemoptysis		1

Physical examination offered little help in the diagnosis of amebiasis, except in patients with amebic hepatitis or liver abscess. (These cases are discussed below.) A few patients had some tenderness in either the right or the left lower quadrant, or both, but it was hardly diagnostic. In 1 case there was a perianal fistula. In another there was evidence of bronchohepatic fistula with pulmonary involvement. In no case were masses palpated. Evidence of weight loss was present in 11 cases. In the cases without hepatic involvement there was elevation of temperature in only 2 cases, the temperatures being 101 and 102°F.

Proctoscopic examination was done in 47 cases. There were minute mucosal hemorrhages of the rectum in 5 cases, in 2 of which trophozoites were obtained from scrapings. In another case, cysts were observed in the stool but not in the scrapings. In the 2 remaining cases, both stool examination and scrapings failed to reveal either cysts or trophozoites. Seven cases showed the typical proctoscopic picture of amebic dysentery — namely, a sharply punched out ulcer crater, with undermined margins and with normal mucosa intervening. In this group, motile trophozoites were obtained from the ulcers in 3 cases. In 2, cysts were recovered. The remaining patients failed to reveal either cysts or trophozoites. Routine examination of the stools showed evidence of cysts in 1 case. There were 8 cases of ulceration with generalized inflammation of the rectosigmoid mucosa in which scrapings from the ulcerated area failed to disclose cysts or motile trophozoites. Cysts were found on routine stool examination in 3 cases, however, and the remainder showed neither cysts nor trophozoites. In 1 patient, there was ulceration, with diffuse granulomatous changes. Scrapings failed to reveal either cysts or trophozoites, and stools were repeatedly normal. All these patients received active therapy, and repeated proctoscopic examinations were done on all; after the treatment there was complete healing.

Reports of incidence of positive proctoscopic findings in amebic dysentery have shown marked variance. Jackman and Cooper[4] observed lesions in 21 per cent of 115 patients. Manson–Bahr,[5] on the other hand, found that 90 per cent of 258 patients had positive proctoscopic findings. An intermediate figure of 42 per cent positive proctoscopic findings was reported by Browne et al.[6] In our group of 60 cases 47 patients had proctoscopic examinations, and of these 43 per cent had positive findings.

Repeated stool examinations were done on all patients. The stools were examined by direct fecal film and also by the zinc sulfate flotation technic. In many cases, the specimens were plated for isolation of Shigella organisms. As many as fifteen stool

examinations were done on some patients. During proctoscopic examination, warm-stage microscopical studies were made of scrapings from the rectal or sigmoid mucosa for trophozoites.

Stools were positive in 46 cases. Of these, 38 showed cysts, and 8 disclosed motile trophozoites of *E. histolytica*. The location and forms of the organisms are presented in Table 3.

White-cell counts, which were taken on all the patients, ranged from 4000 to 10,000 in all cases uncomplicated by liver involvement, except in 1 in which the count was 12,000. The counts in cases of hepatic involvement are discussed below. The differential counts of white cells in the nonhepatic cases were within the normal range except for eosinophilia in 4 cases. The eosinophil count was 10 per cent in 2 cases and 16 per cent in 2 others.

Barium enemas were administered to 28 patients. In this group 19 patients failed to show any abnormalities, and 9 revealed changes on x-ray study. Of these, 2 disclosed spasticity of the entire colon, and 3 spasticity and irregular narrowing of the lower descending colon and sigmoid. One patient showed spasticity of the colon with loss of normal haustral markings to the hepatic flexure and with rigidity of the lower sigmoid. Cecal irregularity was noted in 4. Of the 9 cases with abnormal roentgenologic findings, there were cysts in the stools in 5. No motile trophozoites were found in any of these cases. Proctoscopic examinations in this group were positive in 4 cases, with pin-point hemorrhage in 2, ulceration with normal mucosa intervening in 1 and ulceration with generalized inflammation of the intervening mucosa in 1. In the cases with cecal irregularity, there was normal rectosigmoid mucosa in 3 and evidence of pin-point hemorrhage in 1. Stools were positive for cysts in 1 of these cases.

Considering the extent of literature published about amebic dysentery, comparatively little has been written about the roentgenologic aspects of the disease. Vallarino[7] was the first to call attention to the roentgenologic findings. More recently, Weber,[8] Bell[9–11] and Ikeda[12] have described the x-ray findings. These included varying degrees of irregular narrowing of the lumen of the large bowel. The cecum, which is the most frequent site of positive roentgenologic findings, is characterized by irregularity and deformity. An unusual degree of incompetence of the ileocecal valve, with rapid reflux of barium into the ileum, has been noted. The abnormalities suggest the findings in the ordinary type of chronic ulcerative colitis, aside from the changes of the cecum. There is a tendency, however, for the involvement to be less uniform and for abnormal segments of the bowel to be separated by what appears to be normal bowel. The wall of the large bowel is also relatively pliant and freely movable. The entire roentgenologic aspect of the disease is one of diminished intensity and severity when compared with manifestations of other types of chronic ulcerative colitis. Amebic granulomas have also been described. There are irregular filling defects in the bowel very similar to carcinoma.

The incidence of positive roentgenologic findings in amebic dysentery varies considerably. Browne et al.,[6] reporting on the findings in 141 cases in which barium-enema roentgenologic studies were done, showed a 36 per cent positive roentgenologic change. Edson and his associates,[13] in a series of 20 cases, reported positive roentgenologic findings by barium enema in 80 per cent. Reeves, of Duke University, working with Ruffin of the same institute, in a series of 54 cases with *E. histolytica* in the stool, examined 19 patients by roentgenogram, and abnormalities considered to be indicative of amebiasis were found in 68 per cent.[11] King, of Memphis, observed roentgenologic abnormalities in the large bowel of all 12 cases of amebic dysentery in which examinations were done.[11] In 3 of these cases, x-ray evidence first suggested the possibility of amebic dysentery, and this was later confirmed. In our group examinations on 28 patients revealed that 32 per cent had roentgenologic changes resulting from the amebic infestation of the large bowel. All cases with positive findings had repeated x-ray examinations after therapy, and in each case the findings returned to normal.

TABLE 3. *Location and Form of* E. histolytica *in 60 Cases of Amebiasis.*

Result of Examination	No. of Cases
Cysts found in stools	34
Motile trophozoites found in stools	5
Cysts found in proctoscopic specimen but not in stools	4
Trophozoites found in proctoscopic specimen but not in stools	3

In our series there were 6 patients who were considered to have amebic hepatitis and 1 who had an amebic liver abscess. All these patients complained of pain in the region of the liver that varied from rather sharp and severe to dull and aching. Patients usually complained of pain in the region of the right costal margin, most frequently in the anterior or axillary region and at times posteriorly as well. In 1 case of liver abscess, the complaints and physical findings concentrated interest in the right lower pulmonary area. In 6 of the 7 cases there were acute temperature rises, which were intermittent in type and reached 103 to 104°F. Chills were present in 3 cases. Jaundice was observed clinically in 2 and in 1 was subclinical, the icteric index being 12.6. There was marked weight loss in 6 cases, varying between 10 and 35 pounds. Diarrhea was present in 4 cases on admission. One patient had no diarrhea on admission, but had had a positive history previously. The stools were bloody in 2 cases. The most important clinical

findings were hepatomegaly and marked tenderness over the liver. In 3 cases the liver could not be palpated because of extreme tenderness and rigidity. The spleen was palpable in 2 patients, both of whom had a history of malaria. The total white-cell count was elevated in all but 1 patient. The counts varied from 11,000 to 26,000, with a predominance of neutrophils. One case showed no elevation of white-cell count and no fever, but followed the low-grade symptomatic picture described by Castellani[14] and Hurst[15] and recently classified by Klatskin[16] as chronic hepatitis.

Stool examination showed trophozoites and cysts in 2 cases. In the remaining 5 the stools were normal. Proctoscopic examinations in three cases with negative stools disclosed no disease. Barium enemas were done in 2 cases but were negative. In 2 others complement-fixation tests for *E. histolytica* were positive. Neither of these patients had positive stools, and proctoscopic examination was negative in both. Liver-function tests in 1 case were normal. X-ray films of the chest were done in 4 cases. In 1 there was elevation of the diaphragm. In another a circular demarcated area of density in the posterior portion of the right lower lobe obscured the posterior sulcus and posterior half of the diaphragm.

There is little doubt that emetine is the drug of choice in amebic infestations of the liver. The response to emetine in cases of amebic hepatitis is quite dramatic. The amount used is generally between 0.4 and 0.8 gm. given parenterally in doses of 0.06 gm. daily. When 0.8 gm. is used it is wise to allow a short rest period after the seventh dose. Emetine in sufficient dosage is also the drug of choice in amebic liver abscesses, in which the amount needed is usually much larger. Most of the patients with amebic abscesses previously reported cured with emetine alone received between 0.6 and 0.8 gm. Klatskin[16] recently reported using the equivalent of 1.3 gm. of emetine in 7 cases of the early, acute type. This type of case responds better, generally, than the chronic abscesses. Payne[17] has recently reported, however, the successful use of emetine alone in large chronic abscesses. His 24 cases required an average of 2.4 gm. given over a period of one hundred and eight days. In 1 case he used 4 gm. in one hundred and twenty days.

The indications for aspiration are failure of the patient to show any improvement after 0.8 gm. of emetine and evidence that an abscess near the surface is getting larger under emetine therapy.

The indications for surgical drainage are rupture of an abscess into a serous cavity with the exception of rupture into the pleural cavity, when aspiration in addition to emetine may suffice; superficial abscesses located in the left lobe of the liver; and secondary bacterial infection of the abscess. In bacterial infection, which is an infrequent complication, the use of aspiration, emetine and chemotherapy may eliminate the necessity of operation.

It is also believed that all cases of amebic hepatitis and abscess should be treated with one of the iodine-containing oxyquinolines. This is given usually after the course of emetine. Carbarsone, being an arsenic preparation, has been considered to be contraindicated in amebic liver involvement. This opinion, however, has been questioned.[18]

The treatment of acute or chronic amebic dysentery consists in the use of the following drugs in various combinations: emetine, carbarsone, chiniofon, Diodoquin and Vioform. There is considerable difference of opinion regarding which of these should be used and in what combinations. It is the belief of the majority that emetine administered parenterally, in addition to one or more of the enteric drugs, should be employed. D'Antoni,[19] however, has advocated the use of Diodoquin in doses of 0.63 gm. three times a day for twenty days, without emetine, and has reported 95 per cent cures.

The schedule used at this hospital consisted of 0.06 gm. of emetine daily for six days, 0.75 gm. of carbarsone being given concurrently each day for a week, followed by 1.8 gm. of Diodoquin daily for two weeks. We have also used Diodoquin as advocated by D'Antoni. The effect on the symptoms and laboratory findings was similar in both groups. Rarely were chiniofon or carbarsone enemas administered. We have not used chiniofon extensively, since it often produced rectal burning and severe diarrhea.

Recently, Lewis[20] has advocated emetine parenterally, as well as Vioform orally and in retention enemas in cases of acute and chronic amebic dysentery. The results of this regime in refractory cases have been excellent.

It is our opinion that the immediate results regarding symptoms and laboratory findings will be good in the majority of cases, whatever regime is used. In the refractory cases one may be forced to resort to many types of regimes to obtain good results.

We were unable to carry out any long-range studies on our patients, so that no attempt was made to determine the percentage of relapses. Just which type of treatment will result in the least number of relapses remains to be seen. Amebiasis is a disease in which treatment is difficult to evaluate, and it is often impossible to differentiate reinfections and relapses.

It is well to mention the toxic effects of emetine. There have been reports of death following therapy.[21] The toxic action is chiefly on cardiac and striated muscles. The patient receiving emetine should be on bed rest and should be examined each day by a physician, attention to any irregularity of pulse, soreness of muscles and fall of blood pressure being noted. If available, electrocardiograms should be taken before and during the course of treatment.

When doses of 0.42 gm. or less are used toxic effects are rare. When larger doses are contemplated, it is well to allow sufficient rest periods between courses.

Discussion

The diagnosis of amebiasis often requires extensive study. In many cases routine examinations of stools will reveal the presence of *E. histolytica* as the causative agent. In others, the correct diagnosis may be arrived at only by proctoscopic examination. The appearance of the rectosigmoid mucosa is often quite typical of amebic dysentery. In other cases, the disease is difficult to distinguish from ulcerative colitis due to chronic bacillary infection or that due to idiopathic ulcerative colitis. Scrapings of the ulcers should therefore be done, and the material examined both for the presence of motile trophozoites and cysts of *E. histolytica* in all cases, regardless of the appearance of the rectosigmoid mucosa.

X-ray examination of the large intestine often offers valuable information and may be the first clue that the patient has amebiasis. It also serves to eliminate other diseases, such as carcinoma, and thus has a twofold purpose. We have already described the roentgenologic findings in amebic infestation of the large bowel. Differentiation between amebic granuloma of the large bowel and carcinoma is often difficult. In some cases resections of portions of the bowel have been done with a preoperative diagnosis of malignant tumor, and the specimen has shown amebic granuloma of the bowel.[22–24] It is well to remember that carcinoma may also occur in patients with amebiasis. Reed and Anderson[25] have reported 4 cases with a long history of amebiasis and with lesions of the colon that were thought to be amebic and later turned out to be carcinoma.

Roentgen-ray differentiation of amebic granuloma and carcinoma of the large intestine has been emphasized by Bell,[9–11] who points out that the presence of associated abnormal findings in the cecum favors the diagnosis of amebiasis. When such findings are lacking, a therapeutic test is considered to be indicated if there is any associated clinical or laboratory evidence of amebiasis. Symptoms due to amebiasis show improvement after two weeks of antiamebic therapy.

The value of x-ray and fluoroscopic examination of the chest in cases with liver involvement with and without extension into the lung and pleura has been emphasized by Ochsner and DeBakey[26] and by Sodeman and Lewis.[27]

Demonstration of the etiologic agent in any disease places therapy on solid ground. The finding of cysts and trophozoites of *E. histolytica* depends on many factors: the ability of the examiner to recognize the presence of trophozoites and cysts in the stools, the number of stools examined and the type of examination. The examination of the stools should be made as soon as possible after they are passed, since the trophozoites often die and disintegrate in the stools a short time after they are passed. Cysts should be searched for both by the iodine-stained or hematoxylin-stained films and by the zinc sulfate centrifugal flotation method. The study of purge as well as routine stools is of value. The value of scrapings of the rectosigmoid mucosa has already been emphasized. Nevertheless, a certain percentage of patients with amebiasis will not show either trophozoites or cysts. Sawitz and Faust[28] state that the ameba can be detected with the use of iodine-stained or hematoxylin-stained film, in combination with the zinc sulfate centrifugal flotation method, if five stools are examined, in between 70 and 90 per cent of cases. In our series the etiologic agent was demonstrated in 77 per cent of cases.

Sodeman and Lewis[27] have ably discussed the differential diagnosis and the importance of making an early diagnosis of amebic hepatitis. They were able to demonstrate *E. histolytica* in the stools of 55 per cent of cases of amebic hepatitis and 29 per cent of cases of amebic liver abscess. In our group of 7 cases we were able to demonstrate the causative organism in 2 (29 per cent). In 2 other cases with liver involvement, complement-fixation tests for amebiasis were positive. In both cases treatment was instituted before the results of the tests were obtained. Tests were done at the Army Medical School, Washington, D. C., and it took a few weeks for results to be returned. The complement-fixation test, no doubt, would be of value in cases suspected of amebiasis in which no definite ameba can be found, but as yet this test is not in common usage. We are in complete agreement with Sodeman and Lewis that the diagnosis of amebic hepatitis should be made on a clinical basis alone, even when laboratory examination fails to disclose the causative agent, which should nevertheless be sought for diligently.

D'Antoni[29] has subdivided amebiasis into the following clinical groups: asymptomatic; and symptomatic, including asyndromic and syndromic amebiasis, dysentery (acute or chronic), hepatitis and liver abscesses and involvement of other organs (abscesses of lung, brain and so forth).

We have not attempted to subdivide our cases into these classifications. No cases of asymptomatic carriers were included in our series. It has been our experience that the others often merge. A chronic case may suddenly show acute symptoms; in others, falling into the so-called "asyndromic" or "syndromic" group, the patient may have had dysentery in the past or may develop it in the future. We have listed our findings in patients with liver involvement, and also in 1 with liver involvement and secondary pulmonary involvement. One patient in the series showed a perianal fistula, which appeared at the time of the acute

dysenteric symptoms. We have not seen involvement of other organs.

In our group of patients 53 were from New England. When one considers that this is only one Army installation, that many cases with mild symptomatology are not detected, that many others may have been in symptom-free remissions since discharge from the Army and that the incubation period of the disease may be quite long, it is logical to assume that amebiasis is not unusual in New England. Of our group, 22 patients had received treatment prior to admission to the hospital and had relief of symptoms and yet had recurrences for which they were again hospitalized. This is not to subscribe to a common adage: "Once amebiasis, always amebiasis," but merely to emphasize that the disease recurs. There is a variance of opinion regarding the frequency of recurrence. Mateer,[30] using a single standard ten-day course of carbarsone and chiniofon enemas, reported cure in 97 per cent of 104 patients followed from six months to three and a half years. On the other hand, Lamb and Royston,[31] employing even more intensive therapy with chronic relapsing cases with a history of five months' to five years' duration, found that 91 per cent followed for nine weeks had relapses. It is not the purpose of this paper to discuss the question of recurrences but merely to state that, in our observations, relapses have been quite frequent.

In a certain group of patients with dysentery due to *E. histolytica* no positive findings may be elicited by stool, proctoscopic or x-ray examination. These cases present a difficult diagnostic problem and are often labeled irritable colon, mucous colitis and so forth. In such cases the history often gives the clue. Patients with psychogenic disturbances resulting in diarrhea often have a much older history, and psychogenic causes can often be demonstrated. We also believe that any person who has previously had amebic dysentery, who complains of diarrhea and in whom no known cause for the diarrhea can be demonstrated should be considered as potentially having amebic dysentery and treated accordingly. This policy could also apply to patients without a specific history of amebic infestation who have been in a highly endemic area and in whom likewise no cause for diarrhea can be found. It has been gratifying to see a number of such cases completely clear up under therapy. It is realized that patients with psychogenic disturbances of the bowel have been located in endemic areas and that the symptoms are not due to amebic infestation. In these cases, however, one can generally obtain a definite psychogenic background, and little is lost even though therapy may be given with complete failure.

We should also like to stress the similarity of the appearance of the rectosigmoid mucosa on proctoscopic examination in amebic dysentery and that seen in both bacillary dysenteries and idiopathic ulcerative colitis. Attention has been called to the fiery-red mucosa of acute bacillary infections and the discrete, undermined ulcers of typical amebic dysentery. In the more chronic stages of amebic dysentery and bacillary infections, mixed secondary infestation with the colon bacillus, staphylococcus and streptococcus may so alter the appearance of the mucosa that its specificity is lost and the appearance is indistinguishable from that of typical ulcerative colitis. We therefore believe that if there is a definite history of amebic infection and if stool cultures and examination fail to show a specific etiologic agent, antiamebic therapy is indicated, even though the appearance of the rectosigmoid mucosa suggests idiopathic ulcerative colitis. We have seen 2 cases diagnosed as idiopathic ulcerative colitis in which the patients, who were given symptomatic treatment for six months without relief, showed complete clearing of symptoms and return of the rectosigmoid mucosa to normal when placed on antiamebic therapy.

Summary

Because of the great number of men and women of the armed forces who have lived in areas highly endemic for amebiasis and who now have returned to civilian life, amebiasis will probably be more frequently encountered in post-war civilian practice in New England.

The clinical picture, laboratory findings, proctoscopic findings and roentgen-ray manifestations in 60 cases of amebiasis are reviewed. The diagnosis of amebiasis often requires extensive study, including repeated stool, proctoscopic and x-ray examinations.

The liver is not too infrequently involved in amebiasis, and the etiologic agent cannot be demonstrated in a large percentage of cases.

The proctoscopic visualization of the rectosigmoid mucosa in chronic amebic dysentery may be indistinguishable from that of idiopathic ulcerative colitis.

The similarity of amebic dysentery to functional disturbances, frequently described as "irritable colon," "mucous colitis" and so forth, is discussed. Patients presenting such a symptom complex, who have had a previous history of amebic dysentery or have lived in an area highly endemic for *Endamoeba histolytica* should be given a trial of antiamebic therapy.

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ATYPICAL ADDISON'S DISEASE ASSOCIATED WITH DIABETES MELLITUS*

Report of a Case

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SINCE the description of the syndrome of adrenal cortical insufficiency by Addison in 1855, a review of the literature reveals only 16 accepted cases in which this syndrome appeared in combination with diabetes mellitus. Nearly seventy-five years elapsed after Addison's paper before a case showing this combination was reported by Unverricht[1] in 1926. It has since been recognized that these cases fall into three distinct groups, depending on the time of development of one disease in relation to the other. Thus, there are 4 cases in which, as nearly as could be determined, the two diseases developed simultaneously, 3 cases in which patients with Addison's disease subsequently developed diabetes mellitus and 9 cases in which Addison's disease followed the onset of diabetes mellitus (Table 1).

The following case, in which the diabetes was present for at least two years before the Addison's disease made itself apparent, is reported not only as an additional case of this rare combination of two metabolic diseases but also because of the markedly atypical character of the picture of adrenal cortical insufficiency as it affected the patient.

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K. M., a 20-year-old Irish girl, was first admitted to the hospital on November 1, 1944, in severe diabetic acidosis. The past history was essentially irrelevant until 4 months before admission, when she noted the sudden onset of polyuria, polyphagia, polydipsia, weakness and weight loss. A physician made a diagnosis of diabetes mellitus, gave her a dose of insulin and placed her on a restricted carbohydrate diet, with instructions to return in 1 week. Because she felt somewhat better and did not want to stop work, however, she did not return. Five days prior to admission she failed to observe her diet because she felt very hungry. Two days later she developed a sore mouth, nausea, vomiting and dizziness. On the day of admission she was seen by her doctor because of progression of these symptoms. He administered 35 units of protamine-zinc insulin and 30 units of regular insulin and sent her to the hospital.

Physical examination revealed an acutely ill, dehydrated and lethargic young woman whose mouth contained scattered ulcerated lesions involving the gingiva as well as other mucosal areas. The chest was clear, and the heart was normal. The skin was dry and warm and somewhat loose. The rest of the physical examination was negative.

The blood pressure was 115/65, and the pulse was of good quality.

The urine showed a ++++ test for sugar, a ++++ test for acetone and a ++ test for diacetic acid. The blood sugar was 360 mg. per 100 cc., and the carbon dioxide combining power 32.1 vol. per cent.

A diagnosis of diabetes mellitus and diabetic ketosis was made, and the patient was started on treatment with continuous intravenous fluids and insulin. During the following 20 hours she received a total of 390 units of regular insulin and 5660 cc. of 5 per cent glucose in physiologic saline solution, at which time the blood sugar had fallen to 130 mg. per 100 cc. and the carbon dioxide combining power had risen to 48 vol. per cent. The urine showed a + test for sugar, with no acetone or diacetic acid. By that time the oral condition had become much worse, and the temperature

had risen to 101°F. She was placed on sulfadiazine for 2 days, followed by 4 days of penicillin, with good results. Meanwhile, an attempt was made to regulate the diabetes with the use of protamine-zinc insulin. She was placed on a daily diet of 250 gm. of carbohydrate, 90 gm. of protein and 80 gm. of fat (2080 calories), and on this diet she required 70 units of protamine-zinc insulin to regulate her sufficiently well for discharge. It was on this regime that the patient was referred to the diabetic clinic for further care.

For the next 2 years the patient attended the diabetic clinic but was irregular in her appearances and was consequently difficult to control. At various periods the insulin dosage had varied from 40 to 70 units of protamine-zinc insulin. She had no further episodes of acidosis, but the urine frequently showed a ++++ test for sugar. She admitted dietary excesses and apparently had no insight whatever into her condition. Three weeks before the second admission she was given 100 units of protamine-zinc insulin, but during the succeeding week she had four episodes of mild hypoglycemic shock on successive mornings. Two weeks before admission she was placed on 25 units of protamine-zinc insulin combined with 50 units of regular insulin each morning and had no further episodes of hypoglycemic shock. She stated, however, that for several mornings she had been feeling weak, dizzy and tired.

On the morning of October 31, 1946, the patient awakened feeling weak, dizzy and nauseated. She was aroused with some difficulty but was unable to eat her breakfast. She was given a glass of orange juice and the regular morning dose of 50 units of regular and 25 units of protamine-zinc insulin. Shortly thereafter she became much more drowsy and lethargic, whereupon her physician was called. Under the impression that this represented impending diabetic coma she was given 30 units of regular insulin, after which she became unconscious and totally unresponsive to stimulation and was immediately sent into the hospital.

Physical examination revealed an acutely ill young woman who was completely unresponsive. The pharynx was slightly inflamed, and the lips were dry, with crusted sores at the corners. The tongue was moist. The eyeballs were normal in consistence. The lungs were clear. The apical impulse could not be felt, but there was no cardiac enlargement to percussion. The heart sounds were of good quality. The pulmonic second sound was greater than the aortic second sound. Sinus tachycardia at a rate of 140 per minute was present. Examination of the abdomen was negative. The skin was cool and dry. There was no pigmentation of the skin or mucous membranes, and there were no dark freckles. The deep reflexes were hypoactive.

The pulse was small and easily compressible. The blood pressure was 90/54.

When seen in the emergency room the patient seemed to be suffering from insulin shock. This impression was further borne out by a urine examination, which showed no sugar and no acetone. She was then given 50 cc. of 50 per cent glucose in distilled water intravenously, without dramatic improvement. This therapy was repeated, and directly after the injection the patient became conscious. Shortly thereafter the urine was again tested and again found to be free of sugar and acetone. Because she still appeared somewhat lethargic, another 25 gm. of glucose was given intravenously, after which she was taken to the ward, where the urine was again examined and showed a ++++ test for sugar with no acetone. She was quiet and still lethargic but was able to answer questions rationally, after a short delay.

Examination of the blood on the next morning revealed a hemoglobin of 68 per cent and a white-cell count of 7700, with a normal differential. The blood sugar was 215 mg., the cholesterol 215 mg. and the urea nitrogen 18 mg. per 100 cc. The sedimentation rate was 42 mm. (Westergren) in 1 hour.

The temperature was 101°F., and the patient had no specific complaints except for marked weakness and lassitude. The blood pressure was 98/60, and physical examination was otherwise entirely negative. She was given no insulin, and the urine was examined at regular intervals. During the latter part of the day she appeared very drowsy but did not sleep. She refused to eat more than small amounts at any of her meals. A blood culture was taken in an attempt to explain the fever, but this was later reported to have been negative. An x-ray film of the chest showed normal lung fields and a small heart.

On the next day, the patient appeared even more drowsy and refused everything by mouth except small sips of water. An afternoon urine specimen showed no sugar but gave a ++++ test for acetone, whereupon she was given 5 per cent glucose in physiologic saline solution alternated with physiologic saline solution parenterally. The urine rapidly became acetone free, and the patient became more alert and responsive. After 1600 cc. of fluids had been administered the intravenous drip was discontinued. On November 3 she ate much better, and the fractional urine specimens showed a ++++ test for sugar, on each occasion, with no acetone. The rectal temperature was somewhat lower but still ranged between 99 and 100°F. Physical examination was again essentially negative. She had been placed on a regular diet and on November 4 was started on 10 units of regular insulin each morning. On that day the urine specimens taken at 8 and 11 o'clock showed a +++ test for sugar, with no acetone, and she was given an additional 20 units of regular insulin at 11:30 a.m. At 3 p.m., while in the dentist's chair, she suddenly went into a shock-like state and was taken to the ward, where she was seen by an intern and found to be unresponsive, even to painful stimuli. The pupillary reflexes were active, and the extremities were cold and moist. The pulse was regular at about 80 per minute. Blood was drawn for a sugar determination, which was later reported to be 175 mg. per 100 cc., and 25 gm. of glucose was injected intravenously. The patient responded rapidly, becoming awake and oriented within a few moments. A urine specimen at that time showed a + test for glucose and no acetone. After this episode she remained apparently quite well for the next four days. On a regular hospital diet with 10 units of regular insulin daily the urine persistently showed a ++ to +++

TABLE 1. *Previously Reported Cases of Addison's Disease and Diabetes Mellitus.**

AUTHOR	YEAR REPORTED	SEX	AGE	PATHOLOGICAL DIAGNOSIS
Patients with simultaneous diabetes and Addison's disease:				
			yr.	
Arnett[3]	1927	F	39	Atrophy
Levy-Simpson[4]	1932	M	16	Atrophy
Gowen[5]	1932	F	54	Atrophy
Nix[6]	1943	M	39	Atrophy
Patients in whom Addison's disease developed first:				
Rhind and Wilson[7]	1941	F	32	Atrophy
Thorn and Clinton[8]	1943	M	23	?
Soffer and Sorkin[2]	1945	M	42	?
Patients in whom diabetes mellitus developed first:				
Unverricht[1]	1926	M	32	Tuberculosis
Umber[9]	1928	F	52	Tuberculosis
Rowntree and Snell[10]	1931	M	34	Atrophy
Rowntree and Snell[10]	1931	M	—	Atrophy
Rogoff[11]	1936	M	25	Atrophy?
Bloomfield[12]	1939	M	30	?
McCullagh[13]	1942	M	—	—
Bowen et al.[14]	1942	F	76	Tuberculosis
Bickel[15]	1945	M	35	?

*Modified from Soffer.[2]

test for sugar. A repeated sedimentation rate was reported as 61 mm. (Westergren) in 1 hour, and the fasting blood sugar was 195 mg. per 100 cc. The temperature ranged between 99 and 100°F. Agglutination tests for typhoid and Salmonella organisms were reported as negative. On November 8 the patient again felt listless and weak and vomited her breakfast. An intravenous infusion was started, and she received 1200 cc. of 5 per cent glucose in isotonic saline solution. During the infusion the symptoms disappeared, and she felt much better, retaining the noon and evening meals. The urine during the day was acetone-free and gave a +++ to ++++ test for sugar. On the next morning she again awakened feeling listless and nauseated. After she had vomited her breakfast another intravenous infusion was started, 5 per cent glucose in isotonic saline solution being used. This was allowed to run for approximately 36 hours, during which the symptoms disappeared and she was again able to eat well and retain all her meals.

It was apparent that this was not an ordinary case of diabetes mellitus. The blood pressure was persistently obtained at a level of 90/54 or less. At the same time the radial pulses were hardly palpable. These factors, in addition to weakness and gastrointestinal disturbance, suggested the possibility of adrenal cortical insufficiency complicating the diabetes. Further questioning of the patient revealed that for the preceding year she had become more aware of increasing weakness and gradual loss of weight. She stated that prior to the present admission the weight had been 116 pounds. On November 11 the weight was 108 pounds. Another factor suggesting the diagnosis of Addison's disease was the rapid improvement in the lethargy and nausea and vomiting following the intravenous administration of glucose and saline solution. With this diagnosis in mind, blood was drawn for serum sodium determination, a plain film of the abdomen was taken, and she was tested with tuberculin. The film did not reveal adrenal calcification, and the intradermal tuberculin tests were negative up to a 1:100 dilution. Meanwhile, the patient had been changed from regular insulin to 30 units of protamine-zinc insulin each morning, with a subsequent diminution in the urinary sugar excretion and with no untoward effects. The low-grade elevation of temperature persisted, as did the elevated sedimentation rate. X-ray films showed minimal thickening of the lining membrane of the right maxillary sinus.

After discontinuance of the intravenous infusion on November 11 the patient did well. She was ambulatory, ate well and appeared cheerful. The urine specimens continued to show sugar, although she was on 30 units of protamine-zinc insulin daily. On November 16 she again began to complain of nausea, vomiting, weakness, lethargy and severe abdominal pain limited to the epigastric region, without radiation. A hypodermoclysis of 5 per cent glucose in isotonic saline solution was started, but the symptoms persisted. The urine was free of acetone and gave ++ to +++ tests for sugar on repeated testing. Physical examination revealed the blood pressure to be 68/50 and the pulse to be extremely weak. The lungs were clear, and the abdomen was soft and nontender to palpation, with no areas of spasticity. On November 18 the hypodermoclysis was removed, and an intravenous infusion of 5 per cent glucose in isotonic saline solution was started. In addition she was given 5 mg. of desoxycorticosterone acetate hypodermically, twice daily. The clinical response was rapid and dramatic. By the next morning she was no longer nauseated and felt stronger. She ate small amounts of food, and the epigastric pain had disappeared. After 2 days of desoxycorticosterone acetate and intravenous therapy she was asymptomatic, and the blood pressure had risen to 100/60. At that time the blood sodium, as determined from a specimen drawn on November 15, was reported as 120.7 milliequiv. per liter, which appeared to confirm the diagnosis. Because of a lack of pigmentation, however, it was decided to establish the diagnosis more firmly. To this end the patient was treated with 6 gm. of supplementary salt in addition to 4 mg. of desoxycorticosterone acetate daily for a period of 11 days, at the end of which the blood sodium was 139.6 milliequiv. per liter — a value well within the normal range. The hematocrit reading was 29 per cent, and the serum chloride was 104 milliequiv. per liter. With these values as a base line, the desoxycorticosterone acetate was discontinued, and the patient was given a salt-deprivation test, after the kidney function, as determined by the urine concentration test and the phenolsulfonephthalein excretion test, had been shown to be normal. On December 1 she was placed on a diet containing 0.6 gm. of sodium a day. On the 7th day of this diet she began to complain of severe nausea and weakness. She appeared to be exhausted and to have lost weight. On the next day she was much worse and vomited several times. The blood pressure had fallen to 78/50, and it was found that she had lost 6 pounds during the course of the test. The hematocrit reading had risen to 41 per cent. The serum sodium had fallen to 127.6 milliequiv., and the serum chloride to 74.5 milliequiv. per liter. In spite of an intake of only 1.5 gm. of sodium chloride daily, the daily urinary output of sodium chloride was at no time below 4 gm. These changes are presented graphically in Figure 1.

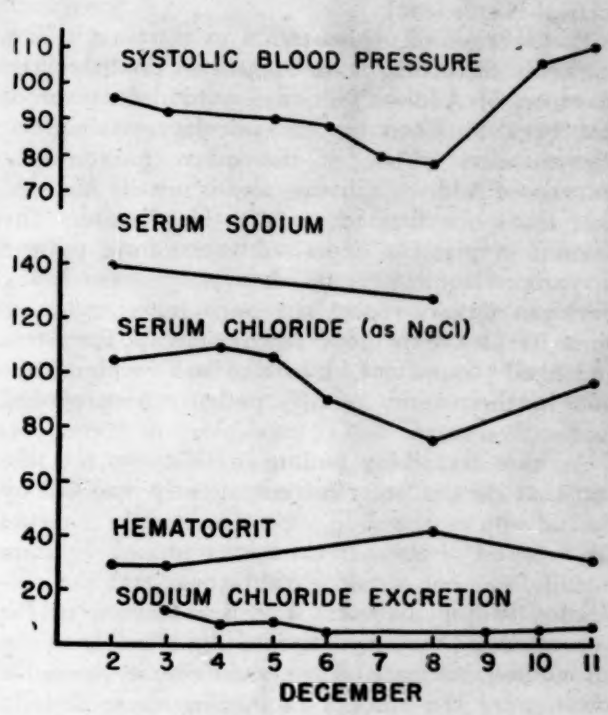

FIGURE 1.

Treatment with 5 mg. of desoxycorticosterone acetate intramuscularly was immediately started twice daily, with an intravenous infusion of 5 per cent glucose in physiologic saline solution. The response was again dramatic, with rapid disappearance of the symptoms by the next day. The blood pressure rose to 110/55, and the patient began gaining weight, was able to eat and rapidly regained strength and vigor. From then until discharge on December 22, she was symptom free and felt better than she had at any time during the previous year. The protamine-zinc insulin was gradually increased until she was receiving 45 units daily, with no deleterious effects and the urine still contained about 1.0 to 1.5 per cent of sugar each day. The dosage of desoxycorticosterone acetate was slowly reduced to 1 mg. intramuscularly daily, and the supplementary salt intake was maintained at 6 gm.; on this routine she was discharged and referred to the diabetic clinic for continued observation.

DISCUSSION

The salt-deprivation tested used in this case was described by Harrop, Weinstein, Soffer and Trescher[16] in 1933. Soffer[2] states that the two findings that make the diagnosis of Addison's disease conclusive are an excess of urinary salt excretion over the intake and a fall in the level of the serum sodium. It was determined to keep the patient on this test diet until she showed some signs or symp-

toms of adrenal cortical insufficiency. She was carefully watched, with frequent determinations of the urinary sodium chloride output, the blood sodium chloride level the serum sodium and the hematocrit. Blood-pressure readings were made twice daily, and the patient was kept at bed rest. It can be seen that on the basis of sodium chloride intake, it was not until the seventh day that she developed the typical signs and symptoms of adrenal cortical insufficiency.

The absence of pigmentation in this case was a markedly disturbing feature and cast doubt on the diagnosis of Addison's disease until definite proof had been obtained by the salt-deprivation test. Pigmentation is one of the most characteristic features of Addison's disease and is usually the sign that leads one first to suspect this disease. The amount of pigment deposited varies from patient to patient: some patients show only a few black freckles. Others report the appearance of many more freckles than they had previously. Rowntree and Snell[10] found only 1 case of lack of pigmentation in their series of 108 patients with proved Addison's disease.

Another disturbing finding in this case was the fact that the diabetes was only slightly modified by the advent of the Addison's disease. In view of the relation of the adrenal cortex to carbohydrate metabolism, one would expect considerable modification in the diabetes, with a reduction of the hyperglycemia and glycosuria and a lowering of the insulin requirements. Unverricht's[1] case showed a lowering of the amount of insulin required daily from 40 units to 5 units, Rogoff's[11] case a decrease of from 48 to 60 units to 5 to 10 units, Bloomfield's[12] case a decrease from 40 units to 8 units, and Bickel's[15] case a decrease from 50 units to 10 units daily. At the time the patient left the hospital, although she was receiving 45 units of protamine-zinc insulin daily, the urine specimens continued to show a ++ test for sugar, with a daily average excretion of 1 to 1.5 per cent of glucose. The 45 units represents only a slight lowering from the insulin requirements of the preceding two years, which averaged approximately 65 units daily.

In spite of these discrepancies, the diagnosis of Addison's disease appears definitely established on both clinical and laboratory grounds. The poor response to intravenous administration of glucose, given for the insulin shock at the time of admission, should perhaps be considered the first clue that this was not a clear and simple case of diabetes mellitus. Whereas ordinary patients with insulin shock respond rapidly and dramatically to the intravenous administration of glucose, this patient did not and was still somewhat lethargic and disoriented after she had received 75 gm. of glucose by vein. This response is in keeping with the course of Addison's disease, since patients with adrenal cortical insufficiency are markedly sensitive to insulin and go into much deeper shock than ordinary diabetic patients given a similar overdose.

The possibility that this patient was suffering from a combination of diabetes mellitus and Addison's disease dawned on the clinicians when it was realized that the radial pulse was nearly impalpable although the general condition was satisfactory. Then the combination of asthenia with a history of weight loss, hypotension and gastrointestinal disturbances manifested by nausea, vomiting and abdominal pain became significant. This, in association with the marked improvement that followed the administration of salt and desoxycorticosterone acetate, suffices to justify the diagnosis. When to this are added the low blood sodium and the typical response to the salt-deprivation test, with the fall in the blood chlorides and serum sodium, the lowering of the blood pressure, the rise in the hematocrit and the continued daily loss of more sodium chloride in the urine than was being ingested, it appears that the diagnosis of Addison's disease was definitely established.

Summary

A case of atypical Addison's disease associated with diabetes mellitus is reported, and the literature concerning this rare combination is briefly reviewed.

The significance of the salt-deprivation test in combination with the clinical and laboratory findings as evidence for the diagnosis is discussed.

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FURTHER OBSERVATIONS ON THE OCCURRENCE OF STREPTOCOCCI OF GROUPS OTHER THAN A IN HUMAN INFECTION*

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THE occurrence of streptococci of groups other than A is rare in upper respiratory infections such as scarlet fever, tonsillitis and septic sore throat. These streptococci, however, are frequently isolated from sporadic infections, including septic abortion (Hare,[1] 1937), puerperal fever (Fry,[2] 1938), meningitis (Rantz,[3] 1942), urinary infections (Porch,[4] 1941), subacute bacterial endocarditis (Wheeler and Foley,[5] 1945) and miscellaneous conditions (Wheeler and Foley,[6] 1943). The predominant role of Group A streptococci in the over-all pattern of streptococcal disease in man is not disputed. The intention of the present communication is to re-emphasize the potential significance of the streptococci of groups other than A, which are too frequently disregarded by the medical bacteriologist.

During the past two years the serologic groups (Lancefield,[7] 1933) of streptococci isolated in 118 cases of miscellaneous infections occurring in children and adults have been classified. These cases represent but a small percentage of the total patients with streptococcal illnesses admitted to the various institutions from which the data for this study were collected. The sample is selected in that only cases thought likely to be nonrespiratory in origin were included, in view of the difficulties involved in assaying the significance of streptococci of groups other than A isolated from the upper respiratory passages.

Such organisms were isolated in 95 (80 per cent) of this series of 118 cases. Of these 95 strains, a total of 77 (81 per cent) belonged to groups B, C–G, D, E, F and K. Concentrated extracts of the remaining 18 strains, all alpha streptococci, did not precipitate with antiserums for groups A–M. Fourteen of these unclassified strains were isolated in cases of subacute bacterial endocarditis.

Streptococci occurred as pure cultures in a total of 93 cases (79 per cent). Of the strains other than Group A, 72 (75 per cent) appeared as pure cultures in primary isolation (Table 1).

The streptococci most frequently encountered in this study were those of Group D. The frequency with which this group was isolated is due in part to the number of cases of urinary infection and subacute bacterial endocarditis included in the series. However, even if these 34 cases are omitted, Group D is second only to Group A in frequency of occurrence.

Of the remaining 16 strains of Group D streptococci, 4 were isolated from patients with intra-abdominal abscesses, and 4 from patients with postoperative peritonitis. Group D streptococci occurred as pure cultures in 3 of the former and in 2 of the latter cases. The other 3 strains were isolated in combination with *Escherichia coli*. All 8 patients were adults.

The other 8 strains of Group D streptococci, with the exception of a strain isolated in a case of septic abortion, were recovered from children. It is of interest that in streptococcal septicemia, Group D organisms occurred with about the same frequency as Group A in these cases (Table 1).

Streptococci belonging to groups B, C–G, E, F and K were encountered in infections occurring in adults as well as children. The majority of strains occurred as pure cultures. Groups H, L and M were not encountered in this series.

The streptococci isolated from patients with subacute bacterial endocarditis deserve comment. There were 34 cases in this series. Group D streptococci were isolated from blood cultures in 19 (56 per cent) of these cases, Group K in 1 (3 per cent), and serologically unidentified strains in 14 (41 per cent). Of the last group, 6 strains (18 per cent) synthesized a polysaccharide in 5 per cent sucrose broth but not in 5 per cent raffinose broth, fermented inulin but not raffinose and otherwise seemed to fulfill the criteria for "*Streptococcus s. b. e.*," as described by White[8] (1944), Niven, Kiziuta and White[9] (1946) and White and Niven[10] (1946). Of the remaining strains in this group, 5 (14 per cent) seemed to be "*Str. mitis*," and 3 (9 per cent) were "*Str. bovis*." None of the "*Str. bovis*" strains hydrolyzed argenine, and only 1 strain of "*Str. mitis*" attacked this amino acid. This latter strain could be differentiated from "*Str. s. b. e.*" only by its inability to change the viscosity of 5 per cent sucrose broth and its failure to ferment inulin (Table 2).

As observed by Foley and Wheeler[11] in 1945, reaction on horse-blood agar, with the exception of Group A (Lancefield[12]) and Group N (Sherman, Smiley and Niven[13]), does not necessarily correlate with serologic group. Alpha and beta strains were found in groups B and E, whereas alpha and gamma strains were encountered in groups F and K. Strains belonging to Group D exhibited the greatest variation; alpha, beta and gamma reactions were

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observed on primary isolation of streptococci belonging to this group. Also in this group successive strains isolated from the same patients or different colonies in a single primary culture frequently showed variable reactions on horse-blood agar. One strain belonging to Group C–G — streptococci that ordinarily produce soluble hemolysin (Todd,[14] of cultures cannot be ascertained if only colonies giving a beta reaction on blood agar are studied. This probably accounts for the failure to isolate organisms of groups E, H and K from normal throats during a survey of streptococcus carriers, as reported recently by the Commission on Acute Respiratory Diseases.[16] In the present study, for

TABLE 1. *Serologic Classification of 118 Strains of Streptococci Isolated in Cases of Human Infection.*

SOURCE OF CULTURE	No. of Cases	SEROLOGIC GROUP								TOTAL INFECTIONS FROM GROUPS OTHER THAN A
		A	B	C-G	D	E	F	K	UNCLASSIFIED*	
Septic wounds	11	6		4	1					5 (45%)
Abscess and peritonitis	17	4	1		8		1	2	1	13 (77%)
Empyema	11	3	1	1	1	1	2	1	1	8 (73%)
Otitis media and mastoiditis	7	5			1			1		2 (29%)
Septicemia	13	4	1	1	3	1		1	2	9 (69%)
Meningitis and brain abscess	6	1	2		1			2		5 (83%)
Septic abortion	3		2		1					3 (100%)
Urinary infection	16		1		15					16 (100%)
Subacute bacterial endocarditis	34				19			1	14	34 (100%)
Totals	118	23 (19%)	8 (7%)	6 (5%)	50 (43%)	2 (2%)	3 (3%)	8 (7%)	18 (15%)	95 (80%)
Strains isolated in pure culture	93 (79%)	21 (92%)	8 (100%)	5 (83%)	32 (64%)	2 (100%)	3 (100%)	7 (88%)	15 (84%)	72 (75%)

*No precipitation with antiserums for groups A–M.

1934) — exhibited a gamma variant in primary culture (Table 3).

The etiologic relation of streptococci of groups other than A to disease in human beings admittedly is not so clear-cut as could be desired, since a specific immune response in the host has not yet

TABLE 2. *Serologic Classifications of 34 Strains of Streptococci Isolated from Patients with Subacute Bacterial Endocarditis.*

GROUP	No. of Strains		Percentage
D		19	56
K		1	3
Unclassified		14	41
Str. s. b. e.	6		18
Str. mitis	5		15
Str. bovis	3		9
Total		34	

been demonstrated against them. Such streptococci, except for certain strains of Group C–G, do not produce erythrogenic or soluble toxin (Pomales–Lebrón,[15] 1940), streptolysin or fibrinolysin,[12] as measured by the technics in use today. However, their isolation, usually in pure culture from suppurative or generalized infection, seems to be indicative of their etiologic significance. Although the results reported here are based on single-colony fishings, except in cases in which the primary culture showed more than one type of colony, it is unlikely that streptococci of groups other than A could occur so frequently as commensurals with Group A streptococci of the same blood-agar reaction.

It is evident from the results of the present study and those reported elsewhere[11] that the incidence of streptococci of groups other than A in a given series example, only 21 (25 per cent) of 82 strains classified into serologic groups other than A gave beta reactions on blood agar.

The frequent occurrence of these streptococci in suppurative or generalized infection is in marked contrast to their relatively low incidence in upper respiratory disease. The low carrier rate, together with the further observation that this carrier rate is not subject to the seasonal changes observed in that for Group A streptococci,[17] suggests that the epidemiology of infection due to these organisms is different from that in disease caused by Group A

TABLE 3. *Reaction of Streptococci Isolated in Human Infection on 5 Per Cent Horse-Blood Agar.*

SEROLOGIC GROUP	No. of Strains			Total
	ALPHA	BETA	GAMMA	
A	0	23	0	23
B	3	5	0	8
C-G*	0	6	1	7†
D	28	9	16	53†
E	1	1	0	2
F	2	0	1	3
K	8	0	1	9†
Unclassified	18	0	0	18
Totals	60 (49%)	44 (36%)	19 (15%)	123

*All strains trehalose positive.

†Some strains presented more than one type of reaction on primary culture.

streptococci. An epidemiologic grouping, such as that commonly seen in cases of infections due to Group A organisms, is a rare occurrence. The majority of infections caused by streptococci of groups other than A are probably endogenous in origin rather than the result of person-to-person transmissions, the immediate precipitating factor disposing to such infection residing in the host

rather than the parasite.[18] This is apparent in postoperative infection and in subacute bacterial endocarditis.

The occurrence of the infection with organisms of groups other than A, furthermore, indicates that the "pathogenicity" of the streptococcus is not entirely dependent on serologic characteristics and emphasizes the lack of knowledge concerning the fundamental mechanics of streptococcal infection.

Summary

A classification of the streptococci isolated from 118 cases of miscellaneous suppurative or generalized streptococcal infections occurring in children and adults revealed that 95 (80 per cent) of these strains were of groups other than A. Strains belonging to groups D, B, K, C–G, F and E were encountered in that order of frequency; 72 (75 per cent) of these strains occurred as pure cultures on primary isolation. Serologically unclassified alpha streptococci were isolated from this series about as often as Group A strains.

The predominance of Group D streptococci can be accounted for in part by the number of cases of urinary infection and subacute bacterial endocarditis in the series. In 34 cases of the latter, Group D streptococci were isolated in 19 (56 per cent), Group K in 1 (3 per cent) and serologically unclassified alpha strains in 14 (41 per cent). Six of these serologically unclassified strains appeared to be "*Streptococcus s. b. e.*"

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MEDICAL PROGRESS

PRACTICAL CONSIDERATIONS OF VENOUS PRESSURE (Concluded)*

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DIAGNOSTIC VALUE OF REGIONAL DIFFERENCES IN VENOUS PRESSURE

In the older literature on venous pressure almost the entire interest centered on values obtained by determination of the venous pressure in one arm. In recent years, it has been demonstrated that comparison of pressure in various peripheral tributaries of the inferior and superior vena cavae greatly increases the diagnostic value of venous-pressure measurements for certain types of disease. Although the literature on the diagnostic significance of regional differences in venous pressure is somewhat limited, the value of this technic is strongly indicated by those who have used it. One can predict that this approach to the use of venous-pressure determinations will find an increasing scope of usefulness. Table 1 presents a list of diagnostic possibilities for a variety of possible regional venous-pressure determinations. Each of these is discussed in further detail in the following sections. Reference is not made to the technic of measurement of intra-atrial pressure by venous catheterization of the right side of the heart.

Diminished Pressure in All Peripheral Veins

It is well known that in shock (peripheral circulatory failure) the systemic venous pressure is characteristically depressed.[6] Venous-pressure determinations are not ordinarily required for the diagnosis of shock. In fact, the diminished pressure and collapsed state of the veins in this condition frequently make it difficult to insert a needle for venipuncture to obtain blood. Venous pressure in shock may be as low as 10 to 20 mm. of water.[48] Gunther[49] and Henstell and Gunther[50] have shown that in cases of shock there is a lowering of intramuscular and venous pressure before the values for plasma volume and arterial blood pressure are altered. When a venous-pressure apparatus is not available one can follow Fishberg's[48] suggestion and note the poor filling of the superficial veins of the upper extremity when the hand is held below the level of the heart. This clinical observation will suffice to indicate that the venous pressure is low. One would expect the venous pressure to be low in ordinary syncope as well.

Slight temporary depressions in venous-pressure levels may occur normally in a number of procedures: abdominal compression in the normal supine subject may produce a fall in average arm-vein pressure equivalent to 17 mm. of water[3]; normally, the venous pressure falls during the Müller experiment[3]; and hyperventilation produces some fall in venous pressure. Such minor and temporary depressions, which are of no clinical importance, are occasionally noted, and therefore their significance should not be misunderstood.

Elevated Pressure in All Peripheral Veins

The most extensive use of venous-pressure measurements has been made in the study of congestive heart failure. The literature abounds with reports that attest to the value of the procedure in this connection.[1–7] In the past few years a number of studies[36, 51–56] have led to uncertainty regarding the manner in which elevation of venous pressure results and its place in the mechanism of heart failure. This uncertainty about sequence and mechanism does not detract from the practical value of the test.

In failure of the right ventricle alone and in general cardiac failure there is a comparable elevation of pressure in all the systemic veins. Isolated failure of the left ventricle does not influence the venous pressure.[4, 7] At times, when a patient with right ventricular failure improves rapidly with treatment, disappearance of edema and hepatomegaly may lag behind the return of the venous pressure to a normal level.[3, 4] For example, intravenous administration of certain drugs, including aminophylline, mercurial diuretics and digitalis, is known to bring the elevated venous pressure down rapidly. This may be confusing if earlier measurements have not been obtained. Also, in cases of mild heart failure the venous pressure at rest may be persistently normal.[3] Often, confusion can then be dispelled by careful use of the maneuver for demonstration of the hepatojugular reflux previously mentioned. Cases of persisting right ventricular failure in which determination of venous pressure, including abdominal compression, is entirely normal must be rare. In their recent review

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of the subject Winsor and Burch[3] also emphasize the fact that even though physical signs of right ventricular failure are not striking, the venous pressure may be high if it is recorded during rapidly progressing failure. They also found that when the antecubital venous pressure was equivalent to 220 mm. of water or greater, the liver was always found to be enlarged, and that when the pressure reached 250 mm., ascites, leg edema and orthopnea were always present.

The compressed heart is a distinct clinical entity that varies depending on whether the compression is acute or chronic. The striking example of the chronically compressed heart is chronic constrictive pericarditis (Pick disease),[57, 58] which classically produces marked dilatation of veins and striking increase in venous pressure to a level equivalent to 400 mm. of water. Burwell and Blalock[59] have succinctly summarized the data relating to venous pressure in this condition as follows:

> 1. The pressure is high (from 150 to 390 mm. of water in systemic veins . . .).
> 2. This elevation is persistent. It may fluctuate, but it does not return to normal and it may be high for years.
> 3. The pressures in arm and leg are not notably different unless there is considerable ascites, an observation which implies that the obstruction is in the heart and not in a cava.
> 4. The pressure rises with exercise more than it does in a normal subject.
> 5. The pressure rises with the intravenous infusion of saline solution at a rate which causes no rise in a normal person.
>
> (These data are similar to those for patients with heart failure with the exception that the elevation of venous pressure is more persistent when it is due to constrictive pericarditis than when it is due to alterations in myocardial function.)

Acute compression of the heart is always caused by a fluid, which may be pus, sterile exudate or blood.[58] Because of the abrupt onset and shorter duration than that in Pick disease the dilatation of superficial veins is less marked, and the peripheral venous pressure ranges to a level equivalent to 150 to 200 mm. of water. Occasionally, pericardial effusion is subacute or chronic. Beck[58] has proposed diagnostic triads for acute and chronic compression of the heart. For the acute form the triad consists of low arterial pressure, high venous pressure and a small quiet heart. For the chronic form the triad consists of ascites, high venous pressure and a small quiet heart. These aphorisms are well worth remembering. In both acute and chronic cardiac compression the high peripheral venous pressure results from mechanical interference with the diastolic dilatation and filling of the heart and not from heart failure per se.

A constant circulatory finding in obstructive emphysema is increase in venous pressure, which in severe cases may reach a level equivalent to 200 mm. of water or more.[60] This is not necessarily due to cardiac failure, as is commonly supposed, but can be attributed to the striking increase in intrathoracic pressure characteristic of this disease. Failure of the right side of the heart naturally may be an additive factor in certain cases. Presumably, the elevation of pressure in obstructive emphysema is of comparable magnitude in both the leg and the arm veins.

The syndrome of Bernheim is considered by some observers an unusual but distinct entity characterized by systemic venous engorgement without pulmonary congestion.[61] It results not from right ventricular failure due to myocardial weakness but from obstruction to blood flow through the right ventricle because of displacement of the interventricular septum owing to marked left ventricular hypertrophy and dilatation from such conditions as hypertension, aortic valvular disease and mitral valvular disease. The diagnosis is suggested when a patient with left ventricular hypertrophy shows signs of right ventricular failure, — that is, distended veins and increased venous pressure, enlargement of liver, dependent edema and so forth, — with minimal or absent signs of pulmonary congestion.[61] Likewise, the circulation time may remain within normal limits for a considerable period, whereas the venous pressure is appreciably elevated.[61] Although only values for arm venous pressures are recorded in the literature, the nature of the circulatory disturbance suggests that the venous pressure is equally elevated in both the arm and the leg.

Another cause of general elevation of venous pressure has been reported by Mayerson, Long and Giles.[62] They observed that in patients with varicose veins of the legs the pressures in the antecubital and saphenous veins were significantly higher than normal when measured with the patients recumbent. They ascribed this to an increase in blood volume that enables the patient to compensate for the effects of gravity while standing but results in an overcompensated state when he is supine.

Normal Pressure in Arm Veins and Elevated Pressure in Leg Veins

A variety of disorders, mostly by interference with blood flow through the inferior vena cava or its pelvic tributaries, produce a distinctive elevation of pressure in the leg veins in contrast to a normal pressure in the arm veins. Tympanites readily causes such a situation. Particularly significant is the development of tympanites when a tight abdominal binder is in place. In a like manner ascites produces a noticeable elevation of leg-vein pressure. In a typical example the venous pressure in the arm was equivalent to 80 mm. of water whereas the leg venous pressure was equivalent to 250 mm.[63] This is undoubtedly a mechanism whereby ascites may contribute to the formation of edema of the legs. Ascitic fluid must be removed or tympanites relieved before it is possible to decide whether elevated venous pressure in the leg is due to these conditions or some other lesion interfering

with inferior-vena-cava blood flow. Brams, Katz and Kohn[64] have demonstrated that distention of the abdominal cavity of a dog with air can elevate the iliac venous pressure to a level equivalent to 620 mm. of saline solution. Their experiments suggest that artificial pneumoperitoneum in human beings and the so-called "spontaneous valvular pneumoperitoneum,"[65] which results from rupture of an air-containing viscus, could likewise impede blood flow in the inferior vena cava sufficiently to elevate the venous pressure in the leg.

During pregnancy local disturbances in the venous circulation of the lower extremities are quite common, as manifested by the development of varicose veins or the aggravation of varicosities already present; by the appearance of edema in which cardiac, renal, nutritional or endocrine causes are obviously lacking; and by the occurrence of acute thrombophlebitis, usually as a post-partum complication.[66] Studies initiated by Burwell[67] and confirmed by others[66, 68] agree that, although the antecubital venous pressure in normal pregnancy is not significantly different from that in the nonpregnant state, the femoral venous pressure is increased in the latter part of pregnancy. McLennan,[68] in a detailed investigation of 255 pregnant women, made the following observation:

> Femoral venous pressure begins to rise in the early part of the second trimester, rises rather rapidly between the twentieth and thirtieth weeks of gestation, then somewhat more slowly to reach an average peak value at term of approximately 240 mm. of water. It falls quickly after delivery to nonpregnant levels and apparently lies somewhat below the average control level during the puerperal period of bed rest.

This regional difference in venous pressures is believed to be responsible for the venous collateral patterns that frequently develop during pregnancy.[67] Veal and Hussey[66] regard the elevated femoral venous pressure in pregnant women as contributing to the formation of edema of the lower extremities and the incidence of varicose veins in pregnancy as being directly related to the venous pressure in the legs. The major factor responsible for the elevated leg venous pressure is obstruction to venous outflow by the gravid uterus,[66–68] although Burwell[67] believes that inflow of a large amount of blood via the placenta may be an additional factor.

Nearly all types of malignant renal tumors are capable of invading the renal vein and inferior vena cava[69, 70] and may produce obstruction of the inferior vena cava and even invade the heart. In the older literature obstruction of the inferior vena cava was suspected only when evidence of collateral circulation developed. As may be expected, a striking elevation of leg venous pressure occurs in such cases, and its measurement is warranted in the study of a renal tumor when the question of metastatic spread to the inferior vena cava arises. In a typical case Ferris and Blankenhorn[63] noted a leg venous pressure equivalent to 320 mm. of water, whereas the arm pressure was equivalent to only 70 mm. In a similar manner primary liver carcinoma may invade the inferior vena cava[71] and produce obstruction to blood flow, with resultant increase in femoral-vein pressure.[63] Figures obtained in a representative case revealed a leg venous pressure equivalent to 220 mm. and an arm venous pressure equivalent to 50 mm. of water.[63]

Ligation of the inferior vena cava as a means of preventing pulmonary embolism in the presence of phlebothrombosis of the leg or pelvic veins has become an accepted therapeutic procedure.[72] One would naturally expect a striking elevation of leg venous pressure in such cases. In a detailed study of 5 patients after ligation of the inferior vena cava Burch and Winsor[73] noted pressures in the veins of the dorsum of the feet ranging from the equivalent of 170 to 506 mm. of water, with normal antecubital-vein pressure. The venous pressure in the legs had not returned to normal as long as ten months postoperatively and was inversely related to the degree of development of the collateral circulation. In most cases edema of the feet persisted for many months.

Obstruction of the inferior vena cava from thrombosis, thrombophlebitis, pressure from adjacent masses and primary tumor of the inferior vena cava should act much as ligation of the vessel and should selectively elevate the venous pressure of the legs.[63, 74–76] If the obstruction is of slow onset with involvement of the renal veins the resultant picture is one that closely resembles the nephrotic syndrome.[75] Tumors that metastasize to the inferior vena cava may eventually spread or be carried to the heart and may produce elevation of the venous pressure in the arms as well.

The inferior vena cava passes through the posterior portion of the liver in the right costovertebral sulcus. This close anatomic relation explains the fact that localized intrahepatic tumors may cause inferior-vena-cava obstruction with resultant increase in leg venous pressure. Venous pressures given in a representative case were equivalent to 180 mm. of water in the legs and to 40 mm. in the arms.[63] A comparable situation could exist for a single congenital cyst or an echinococcus cyst in the right lobe of the liver.

Ferris and Blankenhorn[63] have described a new sign, which is diagnostic of solitary abscess in the right lobe of the liver. In each of 5 consecutive cases of this lesion they noticed an elevation of pressure in the leg vein, that in the arm being normal. The leg pressures in these cases were equivalent to 140 to 370 mm. of water, whereas the arm pressures varied from 40 to 80 mm. The leg pressure was noted to drop when pus was aspirated from a liver abscess. The authors postulate that an abscess mass may press not only on the inferior vena cava to raise the leg venous pressure but also on bile or portal radicles to cause obstructive jaundice or

signs of portal congestion. The specific value of the Ferris-Blankenhorn sign becomes clear with the demonstration that diseases causing a more or less symmetrical enlargement of the liver, such as fatty liver, portal cirrhosis, acute hepatitis and diffuse carcinomatosis, do not affect the femoral venous pressure, regardless of the size of the organ. Hepatomegaly due to cardiac failure increases both the leg and the arm venous pressures to a comparable degree. Therefore, a clinical picture characterized by infection, an enlarged liver and increased femoral venous pressure with normal antecubital venous pressure is strongly suggestive of a solitary abscess of the right lobe of the liver.

Subphrenic abscess on the right may also cause a specific elevation in the leg venous pressure.[63] The physical findings in this condition and roentgenologic studies of the chest and diaphragm should make possible its distinction from a solitary liver abscess.

It is well known that thrombosis in the femoral and iliac veins frequently follows certain types of abdominal operations, particularly those in the regions of the large veins. During standard abdominal operations in 10 cases Veal and Hussey[22] studied the effects of operative procedures on the pressures in the antecubital and saphenous veins. It was noted that operative manipulations within the abdominal cavity caused an immediate rise in pressure in the saphenous vein without directly affecting the antecubital pressure. These elevated saphenous-vein pressures fluctuated widely throughout the operation, were occasionally of great magnitude and generally returned to normal at the termination of the operation. In a somewhat similar study Davis, Gilman, and Freedberg[77] noted increases in pressure in the veins of the foot in the course of operations on the uterus and its adnexa, with less striking changes during cholecystectomy and inguinal herniorrhaphy. These authors discussed in some detail the possible role of local venospasm as a factor in the rise in venous pressure obtained in the course of certain operations. It is of interest that Davis et al.[77] observed that the severity and frequency of changes in pressure in the leg veins during abdominal hysterectomy, cholecystectomy and herniorrhaphy had about the same incidence as postoperative thrombosis and embolism in these operations — 4.1 per cent, 2.3 per cent and 1.3 per cent, respectively — as reported by Barker and his associates.[78]

During the postoperative period tight abdominal or groin binders may elevate venous pressure in the legs, particularly if marked abdominal distention develops after the binder is applied.[79]

Elevated Pressure in Arm Veins Alone

When the superior vena cava is obstructed and the inferior vena cava patent, the pressure in the antecubital veins is significantly higher than that in the femoral vein and shows an additional temporary increase with the exercise test mentioned above. The same effect may be expected when both innominate veins, both subclavian veins, or both axillary veins are obstructed, although examples of such bilateral venous occlusion must be rare. Katz et al.[80] have reported a case of bilateral innominate-vein thrombosis in which the clinical picture was indistinguishable from superior-vena-cava obstruction except by means of phlebography.

The principal causes of obstruction of the superior vena cava without involvement of the inferior vena cava (superior-vena-cava syndrome) are aneurysm of the arch of the aorta, bronchogenic carcinoma and mediastinal lymphoma.[43, 81] Less frequent causes are metastatic carcinoma of mediastinal lymph nodes, primary thrombosis and mediastinitis.[43, 80, 81]

The completeness, duration and site of the obstruction of the superior vena cava influence the effects noted in the venous circulation. More or less complete obstruction, of course, produces a rather spectacular picture, and most of the reports in the literature are concerned with cases of this type. It has been shown, however, that minor degrees of obstruction also occur and are detectable mainly by venous-pressure measurement.[24, 33, 43] In a study of 35 cases representing the superior-vena-cava syndrome, there were 20 cases in which the venous pressure in the arm was equivalent to 300 mm. of saline solution or more.[43] On the other hand, in 6 cases the venous pressure was equivalent to less than 200 mm. and could be evaluated only by comparison with measurements of femoral-vein pressure, which were significantly lower. In the same study it was pointed out that there may also be a significant difference of venous pressure in the two arms as a result of involvement of one innominate vein as well as the superior vena cava.

With the passage of time, the venous pressure in the arms may go higher, on account of increasing obstruction to the superior vena cava.[82] Under appropriate circumstances such a change may represent an important indication for surgical exploration of the mediastinum. On the other hand, lowering of the venous pressure has been observed to result from development of collateral circulation, shrinkage of a mediastinal tumor by means of x-ray therapy, relief of complicating heart failure, mediastinal decompression[83] and release of the obstruction of the superior vena cava by severing a constricting band.[82]

The site of obstruction of the superior vena cava is important chiefly with reference to the azygos vein. Obstruction above the point of entrance of this vein into the vena cava has less severe effects for the obvious reason that the azygos then serves as part of the collateral circulation. On the other hand, when this vein is also obstructed, blood from the superior-vena-cava system must return to the heart by way of the inferior vena cava. Under these

circumstances, it has been shown that venous flow and therefore venous pressure, in the tributaries of the superior vena cava, respond to certain maneuvers in a way that resembles the normal response in the tributaries of the inferior vena cava.[38, 43] Thus, the venous pressure in the arms rises when the abdomen is compressed, and a paradoxical oscillation of venous pressure with respiration can be observed in the cervical veins and at times in the antecubital veins as well.

In the superior-vena-cava syndrome the increased volume of blood carried by the inferior vena cava as a collateral channel does not influence the pressure in the femoral veins.[43] It remains normal (low by contrast) unless there is some additional factor obstructing flow in the inferior vena cava.

Pressure More Elevated in One Arm Than in the Other Combined with Lower or Normal Pressure in Leg Veins

When there is no cause for localized obstruction to flow in the veins of either upper extremity, it may be expected that venous-pressure measurements obtained simultaneously in both arms will not differ by more than the equivalent of 10 mm. of saline solution.[24] This is also found to be true in cases of heart failure, although the measurements, of course, are higher. Conditions that impede blood flow in the innominate, subclavian or axillary vein on one side without equal change on the other produce correspondingly greater differences in venous pressure in the two arms.

In order of frequency, the main local causes of obstruction of the axillary and subclavian veins are malignant neoplasm (usually intrathoracic), thrombosis secondary to heart failure and thrombosis secondary to trauma or effort of the arm and shoulder.[84] The mechanism of venous obstruction by malignant tumors may be compression of the vein, filling of the lumen by invading tumor cells or thrombosis secondary to such invasion. Thrombosis accompanying heart failure has been reported only in severe cases and is thought to be the result mainly of stagnation of venous blood.[84] The fact that it usually occurs on the left side has been explained by the greater immobility of the left arm in most bedridden cardiac patients and by the longer, more tortuous course of the left innominate vein. Traumatic or effort thrombosis has been explained in various ways by different investigators.[84, 85] It is generally believed that the condition results from compression, torsion or stretching of the subclavian or axillary vein on account of effort involving movements of the shoulder. Many kinds of effort have been blamed, Sampson[85] having disclosed eighteen different acts that have been reported to precipitate the condition. At times there is no history of effort or injury. Since most persons are right-handed, effort thrombosis is more frequently seen on the right side.

The causes for obstruction of one innominate vein without corresponding obstruction of the other are the same as those for the superior-vena-cava syndrome.[80] In a report of venous-pressure studies in 27 cases of aneurysm of the aorta and innominate artery, it was found that 85 per cent of cases showed preponderant obstruction of one innominate vein.[24] It was pointed out that the left innominate vein has a more intimate relation to the aortic arch than the right, so that it is not surprising that obstruction on the left side predominates in cases of aortic aneurysm.

When there is obstruction of the veins draining blood from one arm, the difference in venous pressures in the two arms ranges from the equivalent of 20 or 30 mm. to the equivalent of 300 mm. or more of saline solution.[24, 43, 84] In cases in which obstruction has recently developed, the degree of obstruction can be estimated from the magnitude of the difference in venous pressures; the greater the difference, the severer the obstruction.[84] As a collateral circulation develops, however, the venous pressure on the affected side becomes progressively lower, so that even in cases of complete obstruction of the subclavian vein the pressure may return to the range of normal although not to the level of the unaffected side.[84] In these cases, therefore, the effect of exercise of the hand on venous pressure in the arm is an especially valuable diagnostic adjunct, since the tendency persists for the venous pressure to rise during such exercise on the side of the obstruction.[84]

It has already been mentioned that conditions that alter intrathoracic pressure affect the peripheral venous pressure. In cases of unilateral pulmonary disease without direct involvement of the veins and without attendant change in intrapleural pressure the venous pressure is normal even though the pulmonary lesion is extensive.[86] On the other hand conditions involving one pleural cavity, including pneumothorax, hydrothorax and thoracoplasty, may cause the venous pressure to be higher in the arm on the affected side, presumably because of transmission of increased intrapleural pressure to the innominate vein.[87–90] Less often this type of lesion causes elevation of venous pressure in both arms,[88] and occasionally the effect is noted only in the arm on the unaffected side, possibly because of shifting of the mediastinum with consequent distortion of the venous inflow tracts of the thorax.[91] Usually, the changes in venous pressure that attend pneumothorax and thoracoplasty are transient, subsiding within a few months even though the pneumothorax or thoracoplasty is unchanged.[88] Overholt and Pilcher[89] have emphasized the fact that in their experience unilateral elevation of venous pressure after thoracoplasty is an unfavorable sign and should cause postponement of additional surgery until the measurements are again normal and equal bilaterally.

Pressure More Elevated in One Foot Than in the Other and Normal in Arms

Occasionally, circumstances warrant the determination of venous pressure at the ankle under basal conditions. The study of Tyson and Goodlett[92] indicates that when the femoral vein in one leg is acutely occluded by a clot the venous pressure at the same ankle is elevated with the leg at rest. A similar result could be expected when one iliac vein is occluded. Should the ankle pressure be normal and obstruction still suspected, the exercise test described above[32] should be performed.

Pressure determinations in leg veins are particularly indicated for evaluation of cases of edema of the lower extremities. If the venous pressure is normal in the lower legs after the exercise test, it can be assumed that the major venous channels are patent and the cause for the edema should be looked for elsewhere.[32]

In cases of arteriovenous fistula involving the vessels of the lower extremity, the pressure in the veins near the fistula is elevated, but the systemic venous pressure is normal in the absence of cardiac failure.[93] A similar situation is found when the arm is the site of an arteriovenous fistula.

Dissociation between Pressures in Jugular Vein and General Peripheral Venous System

It has been demonstrated that venous pressures can be determined accurately and safely in the jugular veins. Myerson and Loman[47] have described the technic for measuring pressure in the internal jugular vein, and Hitzig[42] gives in some detail the procedure of utilizing the external jugular vein for determining pressures. These veins are not generally used except in research studies, the indications for determining the pressure in the internal or external jugular vein being limited. Hitzig[42] has demonstrated that this technic is a much more accurate means of studying inspiratory filling of the cervical veins than clinical inspection and palpation.

Loman and Dameshek[34] have reported a case of polycythemia with elevation of the internal jugular pressure in both veins to the equivalent of 300 mm. of water and with a general venous pressure equivalent to only 80 mm. The initial spinal-fluid pressure was equivalent to 380 mm. of water. After venesections totaling 3060 cc. of blood in twelve days the pressures in the internal jugular veins and spinal fluid were normal. Apparently, the plethora of this disease was responsible for the increased internal jugular pressure. Other causes of dissociation between pressures in the internal jugular vein and peripheral veins are also discussed by the same authors. Thrombosis of a lateral sinus would be expected to cause a low or absent pressure in the corresponding internal jugular vein. Obstruction to a lower part of the jugular vascular channel could readily produce dissociation with an elevated internal jugular pressure. An obstructing lesion in the neck or upper mediastinum could readily obstruct one or both jugular veins. An obstructive thrombophlebitis of the internal jugular vein may follow septic throat infections.[94]

The pressure in the antecubital vein may be much lower than that in the veins of the neck in persons with the clinical picture of shock due to sudden onset of severe heart failure.[95] Ordinarily, most patients with cardiac failure have a comparable elevation in both the arms and the external jugular veins.

Elevated Portal-Vein Pressure with Normal Pressure in Arm and Leg Veins

The portal-vein pressure may be determined at laparotomy by insertion of the needle of the venous-pressure apparatus into an omental vein or the splenic vein after delivery of the spleen and before ligation of any of the larger splenic veins.[96] This technic has proved of value in the study of cases of portal cirrhosis and Banti's syndrome.[97] A comparison of the portal venous pressure with the systemic venous pressure — that is, the arm-vein pressure — is particularly valuable. Bellis[96] found the average normal venous pressure to be 100 mm. of saline solution higher than the average pressure in the normal ankle vein, with a range of 140 to 220 mm. in contrast to normal ankle pressures of less than 120 mm. In a case of advanced portal cirrhosis with ascites the portal venous pressure was equivalent to 400 mm. of saline solution. Thompson et al.[97] observed that the splenic-vein pressure ranged from 250 to 500 mm. of water in Banti's syndrome with chronic schistosomiasis and from 270 to 470 mm. in Banti's syndrome associated with cirrhosis. These figures contrast strikingly with supposedly normal splenic-vein pressures equivalent to 100 to 125 mm. of water measured in cases of typical hemolytic jaundice. The arm venous pressures in these cases of Banti's syndrome were essentially normal. It can be concluded that the determination of venous pressures in the splenic vein or in the portal tributary vein is a reasonably accurate although complicated procedure of increasing significance not only in research studies but also in the evaluation of cases for surgical therapy. Blakemore[98] has recently suggested that venous-pressure readings, properly taken at operations designed to shunt the portal blood flow in cases of congestive splenomegaly, are an indispensable aid in localizing the site of obstruction in the portal radicles. The effectiveness of a portocaval shunt in such cases can be shown by determination of the portal pressure before and after the shunt is produced. In 4 cases reported by Blakemore[98] the pressures were equivalent to 310 to 400 mm. of water before and 180 to 240 mm. after the shunt was produced.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 33481

PRESENTATION OF CASE

A forty-six-year-old man entered the hospital because of paroxysmal nocturnal dyspnea.

The patient had enjoyed excellent health until five or six years before admission, when he noted the onset of mild exertional dyspnea. During the three years prior to admission he had occasional frontal headaches. Nine months before admission an overpowering feeling of fatigue and severe exertional dyspnea set in, causing the patient to give up work. He was hospitalized at that time, found to have diabetes and put on a dietary regime with 15 units of insulin a day. Subsequently, he felt improved and returned to work. Five months later he consulted another physician, who stated that he no longer needed insulin and placed him on a vegetable diet. He did not do well. During the month before admission several new symptoms developed: paroxysmal attacks of dyspnea occurring almost nightly, orthopnea requiring two or three pillows, marked ankle edema and precordial pain on effort. The exertional dyspnea became very severe, and he was bothered by frequency and nocturia (five times). A week before admission he had marked anorexia and occasional vomiting. He had lost 60 pounds during the present illness.

The patient had no knowledge of hypertension. There had been no tinnitus, epistaxis or vertigo and no kidney symptoms except gradually increasing frequency during the present illness. The alcoholic intake averaged a pint a day for fifteen to twenty years until eight months before admission, but the food intake had always been good. He admitted that he had had gonorrhea five times and syphilis once about fifteen years before entry. The former was treated with irrigations, and the latter with a styptic pencil.

Physical examination disclosed a well developed and well nourished, slightly dyspneic man sitting up in bed. The fundi showed tortuosity of the vessels, hemorrhages, exudates and blurring of the disks. The neck veins were distended and pulsating. The heart was markedly enlarged with the apex in the anterior axillary line in the sixth intercostal space. There were a Grade III systolic murmur, heard all over the precordium but best heard at the apex, and a blowing diastolic murmur along the left sternal border. The liver edge was smooth and exquisitely tender and extended four fingerbreadths below the costal margin. The spleen was felt three fingerbreadths below the costal margin and was also tender. No ascites was noted. There was marked pitting edema of the ankles.

The temperature was 98°F., the pulse 80, and the respirations 20. The blood pressure was 240 systolic, 160 diastolic.

Examination of the blood revealed a hemoglobin of 14.4 gm. per 100 cc. and a white-cell count of 9100, with 88 per cent neutrophils. The urine showed a +++ test for albumin and a negative test for sugar, and the sediment contained occasional hyaline and granular casts and occasional white cells. A blood Hinton test was negative. The nonprotein nitrogen was 48 mg. per 100 cc. and a phenolsulfonephthalein test showed 10 per cent excretion of the dye in two hours.

An x-ray film of the chest disclosed left ventricular enlargement and considerable pulmonary congestion. There was probably some fluid in the left costophrenic angle. An electrocardiogram showed left ventricular strain and auriculoventricular block.

During the hospital stay the patient was at first irrational but later lapsed into coma. A lumbar puncture on the eighth hospital day revealed an initial spinal-fluid pressure equivalent to 425 mm. of water. The pressure fell to 275 mm. with the removal of 8 cc. The fluid contained 2 red cells per cubic millimeter but no white cells. The protein was 80 mg. per 100 cc. The serum nonprotein nitrogen gradually rose, reaching 130 mg. per 100 cc. terminally, with a carbon dioxide of 20.4 milliequiv. per liter. The uric acid was 10.1 mg., the calcium 7.5 mg. and the phosphorus 4.6 mg. per 100 cc. The blood pressure varied between 260 systolic, 190 diastolic, and 205 systolic, 135 diastolic. The respirations were Cheyne–Stokes in character during almost the entire hospital stay. On the seventh hospital day the temperature suddenly rose from normal levels to 100.8°F. and thereafter varied irregularly between 100 and 101°F. until the twentieth hospital day, when it gradually started to climb, reaching 105.8°F. during the next four days. The pulse rate, from the seventh day on, averaged between 90 and 110, with several brief spikes to 110. The respiratory rate was very irregular, varying from 20 to 30. On the fourteenth and fifteenth days cough was a prominent symptom, and thereafter frequent note was made of rales at the bases. The urine never showed more than a few white cells.

The patient died quietly on the twenty-fourth hospital day.

Differential Diagnosis

Dr. Richard J. Clark: From this protocol we develop the impression of a definite type of patient. He was a forty-six-year-old man who entered the hospital well nourished, in spite of the fact that he had lost 60 pounds in weight. Evidently he had been obese. He admitted that he had had gonorrhea on five occasions. He gave a history of syphilis, which had been treated with a styptic pencil. He had taken a pint of alcohol daily for twenty years. In spite of this prophylactic medication severe hypertension and severe arterial disease developed. At the outset we may assume by definition that he had malignant hypertension. It is also quite certain that he had congestive heart failure of a severe degree involving both the left and right sides of the heart. In addition, he had severe renal disease and died with a picture of terminal uremia. Perhaps I should stop here and stay out of hot water, but I do find a number of intriguing side issues that are of interest to speculate upon.

In the first place, did the patient have a simple malignant hypertension or possibly a pheochromocytoma? The history mentions glycosuria. We do not know definitely that he had diabetes, although there was at one point sufficient glycosuria to require insulin. At the time of entry to the hospital there was no positive evidence of diabetes. In a patient with hypertension and glycosuria, pheochromocytoma is one of the factors to be considered. Ordinarily, pheochromocytoma is regarded as presenting a paroxysmal type of hypertension, of which there is no definite evidence in the case under discussion. We do know that the diastolic pressure ranged between 135 and 190. Green* has reported a series of 51 patients with pheochromocytoma. The interesting thing is that only 14 presented definite paroxysmal hypertension. The other 37 had sustained hypertension, and 4 of these ran a course of malignant hypertension with death from cerebral vascular accidents, congestive failure and uremia. Some hypertensive patients upon whom sympathectomy has been performed have revealed unexpected adrenal tumors at operation. Apparently, this patient was too sick to have had an intravenous pyelogram done, although this would have been of interest. I see no definite basis on which to make a diagnosis of pheochromocytoma, but such a finding at post-mortem examination would not surprise me.

What about the urinary tract? The patient had very little or nothing in the way of urinary symptoms until approximately a month before death. He had no previous history to suggest acute glomerulonephritis at any time. He did have diabetes, and we might wonder about intercapillary glomerulosclerosis, but so far as I am aware that has not been described as an accompaniment of the malignant type of hypertension. The same point may be made regarding infections of the urinary tract. The urinary sediment contained only a few white cells, and at no time did he have any appreciable evidence of true urinary-tract infection. He had gonorrhea five times. The amount of frequency (nocturia of five times) in the last month is in some ways a bit more suggestive to me of an obstruction in the urinary tract than it is of a simple renal lesion. Did he possibly have a stricture, or did he have constriction in the region of the prostate causing back pressure? That is a definite possibility, but the symptoms of hypertension developed a considerable time before the urinary frequency, and I cannot conceive of a hydronephrotic picture giving rise to this situation. All in all, the most probable diagnosis so far as the renal tract is concerned is malignant nephrosclerosis.

What about the cerebral status? One of the differential diagnoses of malignant hypertension with encephalopathy is brain tumor. Could the patient have had a brain tumor? He had a high spinal-fluid protein and eye-ground findings that could have been consistent with tumor. On the other hand he had no localizing symptoms and no severe headache. I can see no reason for making a diagnosis of brain tumor in this case and believe that all the findings, including the spinal-fluid pressure and the spinal-fluid protein, are entirely consistent with malignant hypertension and uremia.

Now we come to the heart, which is one of the stumbling blocks along the line. May we see the x-ray films?

Dr. Stanley M. Wyman: The heart is markedly enlarged, chiefly toward the left and probably chiefly the left ventricle. The aorta is somewhat tortuous. It can be seen in the lateral view, descending close to the posterior chest wall. There is probably a very small amount of fluid in one of the costophrenic sinuses. The hilar shadows are definitely enlarged. Whether this is entirely vascular or whether there are underlying changes in the lymph nodes or possibly in the stem bronchi, I cannot say. We should have two things to verify this point, fluoroscopy and a heavy exposure film. The picture is consistent with congestion, however.

Dr. Clark: What would you say about the aorta? Do you consider it dilated? Can you define the areas of dilatation if there are any?

Dr. Wyman: One cannot make an accurate measurement of the diameter of the aorta, except at the arch, where it does not look dilated.

Dr. Clark: Do you think, from the x-ray point of view, that you can make a reasonable differential diagnosis between left ventricular enlargement in aortic regurgitation and aortic-valve disease as against left ventricular hypertrophy of hypertensive heart disease?

*Green, D. M. Pheochromocytoma and chronic hypertension. *J.A.M.A.* 131:1260-1265, 1946.

DR. WYMAN: Not by x-ray study alone. This is consistent with hypertensive heart disease, but we certainly see the same picture without the enlargement of the hili in aortic regurgitation.

DR. CLARK: The heart was obviously very much enlarged. There was a loud systolic murmur at the apex, which might have been due to organic mitral regurgitation, but with the degree of enlargement it probably represented functional regurgitation. The next item is the diastolic murmur heard clearly along the left sternal border. We can say definitely that this patient did not have free aortic regurgitation. He had no wide pulse pressure and no drop in diastolic pressure. Syphilitic heart disease may be engrafted upon hypertensive heart disease. Did this patient have syphilitic aortitis or aortic-valve involvement in addition to the hypertensive heart disease? The blood serologic findings were normal. Is the spinal-fluid Wassermann test recorded?

DR. TRACY B. MALLORY: No.

DR. CLARK: In cardiovascular syphilis the serologic reaction is positive in 85 per cent or more of cases. This man was relatively young, and I believe that if syphilitic aortic regurgitation had been developing, which would have occurred in the early developmental stage, the serologic reaction would have been positive. Beyond that, the story of syphilis is quite uncertain. Certainly, syphilitic aortic regurgitation could not have accounted for the dyspnea of several years' duration such as this patient had, without being much more full blown than it was. I shall therefore discard any diagnosis of syphilitic involvement of the heart.

Could he have had rheumatic heart disease along with hyertensive heart disease? Such a combination is common. From the x-ray film, if he had rheumatic heart disease, it must have been primarily aortic-valve disease. There was no past history of heart trouble or rheumatism. That does not rule out the diagnosis, but on the law of chances I shall let it go by the board.

How about pulmonary regurgitation giving rise to the murmur? That is a possibility. What about hypertension and hypertensive heart disease as possible causes? The electrocardiogram showed definite left ventricular strain and was consistent with hypertensive heart disease. We know from certain series of cases that aortic regurgitation occurs in conjunction with hypertension in between 2.5 and 7 per cent of cases, without assuming any other disease of the aortic valve. This apparently arises from dilatation of the aorta and aortic ring. If that situation ever occurs, it may well have been present in this case with a considerably dilated heart and a tremendous rise in diastolic blood pressure.

I shall hold to my original diagnosis of hypertensive heart disease. In addition, I believe that post-mortem examination revealed definite evidence of coronary-artery disease. The patient had precordial pain on exertion during the last year of life, and also in the electrocardiogram he showed delayed auriculoventricular conduction. These two factors are reasonable evidence on which to make a diagnosis of coronary disease.

There is one more problem in this museum of difficulties — namely, the enlarged liver and spleen. If we go back in the history we realize that the patient had been taking alcohol in large doses for twenty years. Did he have cirrhosis of the liver in addition to the other troubles? Early cirrhosis may produce a nodular liver such as that described, but I am not aware that cirrhosis of the liver ordinarily causes a tender liver. The liver described in this case is consistent with the liver of congestive heart failure, and without any other definite evidence to tie to, I shall consider it as such.

The matter of the spleen is not quite so easy. The patient had no anemia on entry. There was no evidence of any blood dyscrasia and no abnormal adenopathy or anything of that sort to associate the spleen with. In a cardiac patient with splenic enlargement, particularly with a tender spleen, the first thing to consider is subacute bacterial endocarditis. I have already ruled out the ordinary cardiac lesions upon which subacute bacterial endocarditis is usually engrafted. Against subacute bacterial endocarditis was the absence of fever on entry or other corroborative physical findings. What about splenic infarction? This is one of the other conditions in heart disease that one must consider as a cause for splenic enlargement, but there was no history to substantiate such an episode. There are debates about the occurrence of palpable splenic enlargement from passive congestion. Some authors state that it never occurs except occasionally in childhood. Others say that it occurs on occasion. I shall assume that the splenic enlargement in this case was on the basis of a fairly severe degree of passive congestion.

What about the terminal episode? The patient was febrile during the last two weeks in the hospital. There was no evidence of increasing urinary-tract infection. His exitus was a gradual one, without any sudden episode. I believe that he developed a terminal bronchopneumonia.

Finally, is there any other single diagnosis that can tie up this myriad of findings and symptoms apart from those that I have mentioned? The only one that I can think of is periarteritis nodosa. There are a number of problems that present themselves with this diagnosis. Periarteritis ordinarily runs a relatively rapid course and yet may drag out over a considerable period, but I cannot conceive of its continuing for five years. There was an acute exacerbation, with the appearance of new symptoms, a month before entry. It is possible that periarteritis nodosa set in at that point. Periarteritis is usually a febrile disease throughout,

whereas this patient had fever only terminally. It usually causes a leukocytosis, which was lacking, although examination of the blood revealed 88 per cent neutrophils. He did not show an eosinophilia, but this is by no means essential to the diagnosis. All in all, I consider periarteritis nodosa a remote possibility.

I shall conclude essentially where I started, with the belief that this man had an acute malignant hypertension, possibly based on a pheochromocytoma, associated with malignant nephrosclerosis and uremia, as well as hypertensive and coronary-artery disease with congestive failure.

Clinical Diagnoses

Malignant hypertension.
Uremia.

Dr. Clark's Diagnoses

Malignant hypertension.
Pheochromocytoma?
Malignant nephrosclerosis.
Hypertensive and coronary-artery disease.
Congestive heart failure.
Terminal bronchopneumonia.

Anatomical Diagnoses

Nephrosclerosis.
Hypertrophy of heart.
Multiple pulmonary emboli, with pulmonary infarction.
Chronic passive congestion.
Thrombophlebitis, left leg.
Mural thrombus, right auricle.

Pathological Discussion

Dr. Mallory: Post-mortem examination demonstrated a greatly enlarged heart, which weighed 750 gm., with apparently normal valves and an aorta that showed very little atheroma and no suggestion of syphilitic scarring. The coronary arteries contained a few flecks of atheroma but no points of significant narrowing. Nevertheless, the myocardium revealed a few minute, microscopic foci of absorption of muscle cells although no gross infarction. A marked degree of nephrosclerosis was found in the kidneys. From the histologic point of view they did not show any of the stigmas of malignant hypertension. There were no changes in the glomeruli and no necrosis of the walls of the blood vessels. This does not surprise me very much, since I have never been able to make a satisfactory correlation between the so-called "clinical malignant hypertension" and the so-called "pathological malignant hypertension." Usually, the pathological findings are consistent in patients who die in uremia in contrast to those who die in cardiac failure or from cerebral accidents. Since this patient was certainly approaching uremia at the time of death, I am a little surprised that the findings were not present, but there was no trace of them. The brain was essentially normal. There was no obstruction in the urinary tract.

The surprise of the autopsy was the presence of four massive pulmonary infarcts each in a separate lobe of the lung, and I believe that those were the cause of the terminal fever — at least we found nothing else to explain it. There was evidence that there had been multiple pulmonary emboli, some much older than the ones that caused the infarcts. The liver was enlarged and showed only passive congestion. The spleen weighed 490 gm., which is a marked degree of enlargement for chronic passive congestion, but we found no other explanation for it.

Dr. Clark: How often do you find enlarged spleens at post-mortem examination from passive congestion and heart disease?

Dr. Mallory: Almost always, but rarely enough enlargement to make us confident that they were palpable. A few years ago I checked over quite a series of cases of splenomegaly, and unless the spleen weighs 400 gm. it is rarely felt. It must be three times the normal size before one begins to feel it. The spleen in this case was distinctly larger than that.

Dr. Clark: This case emphasizes a point that I should certainly have mentioned: in any patient with chronic heart failure in whom one suspects bronchopneumonia, one is probably wrong; it is usually pulmonary infarction.

Dr. Mallory: Possible sources of the thrombi were the deep veins of the leg and the calf, and also a thrombus in the right auricle of the heart. I cannot say from which source the pulmonary emboli came.

A Physician: Was any bacteriologic examination done?

Dr. Mallory: Yes; it was entirely negative.

CASE 33482

Presentation of Case

First admission. A fifty-six-year-old man with a six-year history of attacks of wheezing and dyspnea was admitted to the hospital during an exacerbation of asthma.

He had had severe cough and wheezing for two weeks, requiring adrenalin two or three times a day. The dyspnea had prevented sleep. The cough had produced about a cupful of yellow sputum a day, but he had had no fever. He admitted exertional dyspnea for four or five years and had been unable to work for two years. He denied any definite allergy. A maternal grandmother had had asthma.

Physical examination showed a cyanotic, obese man with a barrel-shaped chest. Respiration was shallow and almost entirely diaphragmatic. There were coarse "squeaks" over both lung fields. Moist

rales were present bilaterally. The heart sounds were distant, and the blood pressure was 130 systolic, 80 diastolic. The liver edge was palpated 7 cm. below the costal margin, the upper border being at the sixth rib. There was moderate pitting edema of the ankles.

Examination of the blood revealed a red-cell count of 4,550,000, with a hemoglobin of 9.7 gm., and a white-cell count of 17,200, with a normal differential. The urine showed a +++ test for albumin and had a specific gravity of 1.016. The sediment contained 30 red cells and 40 white cells per high-power field, as well as granular casts. An electrocardiogram showed a normal rhythm at a rate of 80 to 90, with small Q waves in Leads 1, CF_4 and CF_4. A phenolsulfonephthalein test showed 30 per cent excretion of the dye in half an hour and 70 per cent in two hours. The nonprotein nitrogen was 50 mg. per 100 cc.

An x-ray film of the chest disclosed scattered areas of fibrosis in both lung fields. The hilar shadows were moderately enlarged, and there was an area of soft mottled density in the middle portions of both lung fields and at the bases. There was a small quantity of fluid in each pleural cavity.

The patient improved slowly with adrenalin, aminophylline, a low-salt diet and sedation. The urinary sediment showed 200 red cells and 12 white cells per high-power field. He was discharged unimproved on the thirteenth hospital day.

Final admission (ten months later). The dyspnea and cough, which was productive of about a pint of yellow, sometimes blood-streaked sputum, persisted. Nocturia (four times), developed without other urinary symptoms. Three weeks previously the dyspnea and asthma had increased, and twitching movements of the face and extremities had developed.

Examination revealed an extremely ill, cyanotic man. Numerous coarse rales were audible at the left base. Dullness and diminished breath sounds were present at the right base. There were no cardiac murmurs.

The temperature was 99.6°F., and the respirations were 35 to 40. The blood pressure was 180 systolic, 100 diastolic. The pulse was 110 and regular.

Examination of the blood revealed a hemoglobin of 7.5 gm. and a white-cell count of 12,000. The urine gave a ++ test for albumin and had a specific gravity of 1.012; the urinary sediment contained numerous red cells, white cells and casts. The nonprotein nitrogen was 60 to 85 per 100 cc., the blood calcium 7.6 mg., and the phosphorus 17.0 mg. The phosphatase was 5.4 units. An electrocardiogram showed a normal rhythm (100), a PR interval of 0.14 second and a tendency to left-axis deviation. The Q waves were small and the T waves were upright in Leads 1 and 2.

In spite of digitalization, aminophylline, a washed-red-cell transfusion and other supportive measures the patient died in marked respiratory difficulty on the third hospital day.

Differential Diagnosis

Dr. Myles P. Baker: With the facts at hand it seems to me that the house-officer writing a discharge summary at the end of the first admission must have had some doubt regarding just what he had been dealing with in this patient. It is the story of a cyanotic, asthmatic patient who had had attacks of wheezing dyspnea for years and in whom, with a presumptive diagnosis of bronchial asthma, adrenalin had given definite relief. He was later admitted with signs of bronchiectasis and, by description, an emphysematous chest. The question probably came up on admission whether a superimposed bronchial infection was involved or whether there was an element of heart failure, particularly right-sided heart failure, in view of the cyanosis, the apparent enlargement of the liver and the ankle edema. There was a noteworthy absence of hypertension. With further study the electrocardiogram proved to be not that typical of chronic cor pulmonale, with the development of a prominent S wave in Lead 1 and a prominent Q wave in Lead 3, and there were no inverted T waves in the first chest leads. Nor have we certain evidence of cardiac failure. The liver may have been low because of the emphysematous chest. The upper border may have been at the sixth rib. The man was obese, and it is difficult to feel a liver in such a patient who is breathing rapidly. The edema of the ankles may have been due to obesity and local lymphatic obstruction and not to myocardial insufficiency. The finding of evidence in the urinary sediment of a renal lesion is important and is emphasized in this protocol by the statement that on discharge the patient had a persistent and unexplained hematuria. He had renal insufficiency to judge from the one phenolsulfonephthalein test. He had anemia, for which we have no explanation. The leukocytosis may be explained on the basis of bronchiectasis, but that is not definitely established.

The x-ray examination of the chest is important in arriving at a diagnosis. I suggest that Dr. Wyman show these films.

Dr. Stanley M. Wyman: The first two sets of films show mottled density in the upper lung fields, particularly on the right. This is essentially unchanged in the two films taken five months apart. There is a suggestion of some mottling in the left midlung field. I cannot be sure of the disease in the lower lung fields, although there is a suggestion in one or both of the lower lobes. The fluid described in the costophrenic sinuses is not impressive. The heart does not appear to be enlarged; it has no characteristic configuration. The aorta is not remarkable. I can see no definite hilar or mediastinal

masses. The last film, which was taken five months after the first, shows a marked change. The heart now appears to be definitely enlarged, and the enlargement seems to be chiefly left ventricular. There is a good amount of fluid in the right pleural space. The upper lung fields now show mottled density as on the first examination, with new hazy density in the lower lung fields on both sides, probably in the lower lobes.

DR. BAKER: The picture on admission is not that of a prominent pulmonary conus?

DR. WYMAN: No; the hilar shadows are prominent, but there is no definite enlargement of the base of the pulmonary artery. Along the upper heart borders I cannot see any essential change in the appearance of the hilar shadows in the last observation. The main changes have taken place in the lung fields and in the heart size.

DR. BAKER: This patient was not treated with diuretics and apparently not digitalized and was probably discharged with the diagnosis of bronchial asthma and a renal lesion of undetermined nature — that is, probably, some form of nephritis. The most significant features about the final admission are the relentless progress of the disease toward the uremic picture with which he entered the hospital, the rising blood nonprotein nitrogen to confirm this impression, the progressive anemia and the appearance for the first time of arterial hypertension.

The question of diagnosis seems to me to boil down into one or two possibilities. This man may have had bronchial asthma that had been developing in an insidious fashion, in addition to a renal insufficiency that had contributed to his increasing disability of the past few years and ultimately proved fatal, this renal insufficiency being due to one of the usual causes — glomerulonephritis, essential hypertension or pyelonephritis — or to one of the rare causes, such as polycystic kidneys. There is another possibility that would account for both bronchial asthma of years' standing and renal failure, namely, periarteritis nodosa.

In the few moments that remain we should go a little farther into that possibility. About seven or eight years ago Dr. Rackemann[1] reported briefly on eight cases with a combination of bronchial asthma and periarteritis nodosa, four of which died and four were living. He noted that Dr. Greene had reviewed the literature of periarteritis nodosa and found that 8 per cent of patients had asthma, presumably bronchial asthma, although in the discussion of the paper some question was raised whether some of the cases of asthma were cardiac, rather than true allergic cases. A few years before 1936 some observers reported 3 cases of apparently "run of the mill" asthmatic patients who became worse, began to run fevers, developed some of the diverse symptoms of periarteritis nodosa, such as cutaneous manifestations and polyneuritis or renal failure, and died.[2] In the larger reported series of cases of periarteritis nodosa there are usually 1 or 2 in which bronchial asthma is either the chief complaint on admission or very prominent in the past history. The x-ray picture of the chest in this patient as described in the protocol sounds very much like a few lesions demonstrated by chest x-ray study in cases of periarteritis nodosa. I must say that the x-ray findings as Dr. Wyman demonstrates them are not what is described in these well studied cases.[3] In periarteritis nodosa there is usually a more extensive involvement of the hilar region, and a picture consistent with small pulmonary infarcts rather diffusely distributed through the lower lobes, with small pleural effusions. I believe that the development of hypertensive heart disease in the course of a year is important. In a report of cases of periarteritis nodosa from Johns Hopkins Hospital this point was stressed, the authors mentioning that 1 or 2 patients had variable blood-pressure levels, at first moderately high, then normal and then rising rapidly toward the end to high levels at the time of death from bronchopneumonia.[4] The absence of any hypertension ten months prior to this man's death, at a time when he had diminished renal function and hematuria, otherwise unexplained by a lesion in the lower urinary tract, is much against death from glomerulonephritis.

Glomerulonephritis without hypertension, even in very late stages, is rare. It may occur during the latent stage. This man did not have a latent lesion on first admission to the hospital. Even in the absence of some of the more accepted manifestations of periarteritis nodosa, such as peripheral neuritis and coronary insufficiency, I put that disease down as my diagnosis because of the absence of any other good cause for the renal insufficiency and because of the association with chronic bronchial asthma and the rapid progress of the disease and its terminal phase to uremia.

DR. TRACY B. MALLORY: Dr. Burrage, would you tell us your impression?

DR. WALTER S. BURRAGE: I must confess to being the one who had difficulty in writing the discharge diagnosis at the termination of the first hospital entry. There are a few points of interest in addition to what Dr. Baker has brought out. In the first place this patient had a six-year history of asthma with onset at the age of fifty and with no premonitory symptoms. This presumably places him in the so-called "intrinsic group." It was therefore not surprising to find that the intracutaneous tests were negative. He was cyanotic from the onset, had clubbed fingers and later developed edema of the ankles. The hemoglobin was originally 65 per cent, with a red-cell count of 3,100,000. He never had hypertension during the early stages. Fluoroscopy was done on several occasions in an effort to differentiate the role of cardiac failure and pulmonary infection as complications of the asthma. These examinations demonstrated a heart of rela-

tively normal size, but later ones in particular showed definitely increased lung markings radiating to the bases, which, with the purulent sputum, suggested the possibility of severe chronic bronchitis or even bronchiectasis.

We discussed periarteritis nodosa, but decided against it. The red cells that were always present in the urine were in favor of it as well as of nephritis, but there were none of the multiple symptoms that these patients often have. We also had difficulty in arriving at a diagnosis but finally decided on chronic nephritis, intrinsic bronchial asthma, severe chronic bronchitis and questionable bronchiectasis.

DR. MALLORY: Dr. Lerman, have you an opinion?

DR. JACOB LERMAN: I saw the patient on the last admission when he entered in severe congestive failure. He had a long-standing asthma with pulmonary fibrosis and infection. We considered the possibility that the shadow on the right side was consolidation, pneumonia or, more likely, infarction, and discussed the question of vein ligation, but did not carry it out because he was in poor condition. So far as renal disease is concerned, there was the possibility of pyelonephritis. Two urine cultures were reported: one contained pyocyaneus bacilli, and the other abundant colonies of *Staphylococcus albus*. We were uncertain about blaming the renal picture on chronic pyelonephritis. We considered periarteritis nodosa but decided that this diagnosis was untenable without further evidence. One other possibility as a cause of the uremia occurs to me — that is, amyloid disease resulting from long-standing infection. The patient must have had pulmonary emboli in addition to the pulmonary infection of long standing.

DR. BAKER: The absence of eosinophilia is worth commenting on. It should be emphasized that it is found in less than 20 per cent of cases of periarteritis nodosa.

CLINICAL DIAGNOSES

Bronchial asthma.
Cor pulmonale.
Hypertensive and arteriosclerotic heart disease.
Chronic nephritis.

DR. BAKER'S DIAGNOSIS

Periarteritis nodosa.

ANATOMICAL DIAGNOSES

Subacute glomerulonephritis.
Pulmonary emphysema.
Bronchiectasis, right upper lobe.
Bronchopneumonia, terminal.
Cardiac hypertrophy.
Arteriosclerosis, generalized, moderate.

PATHOLOGICAL DISCUSSION

DR. MALLORY: At autopsy the lungs presented a complicated picture. There was extensive bronchiectasis. There was severe pulmonary emphysema, with patchy fibrosis of the lungs, and in both lower lobes there was a very extensive organizing pneumonitis of comparatively short duration — perhaps a few weeks or months, I should estimate.

The next point of interest was the kidneys, which were greatly enlarged, weighing 580 gm. The surfaces were rather pale and dotted with petechial hemorrhages. On microscopical examination there was a typical subacute glomerulonephritis. From the histologic point of view it looked even more acute than subacute. The heart was very markedly hypertrophied, weighed 680 gm. In none of the organs did we find any lesion suggestive of periarteritis nodosa so that subacute glomerulonephritis was probably the chief cause of death.

DR. CHARLES L. SHORT: Was this cor pulmonale?

DR. MALLORY: No; in cor pulmonale a diffuse hypertrophy of all chambers, most marked on the left, is observed.

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THE CHRISTMAS SEAL CAMPAIGN

The annual Christmas Seal Campaign, which this year began on November 24 and lasts until Christmas, serves as a reminder that support for the organized nationwide program against tuberculosis must be forthcoming. The money collected during the month of the campaign provides for such vital activities as mass x-ray examination, laboratory research, rehabilitation and public education; 95 per cent of this income from the sale of Christmas Seals remains in the state where it is collected, 5 per cent being allotted to the National Tuberculosis Association.

Although notable progress in the control of tuberculosis has been made since 1904, when the National Tuberculosis Association was founded, a great deal remains to be done. Thus, in the half century of the Association's existence, the death rate from tuberculosis has declined 80 per cent (representing a saving of 4,000,000 lives), but the disease still ranks seventh among the causes of death, and half a million persons in the United States — approximately 50 per cent of whom are known to health authorities — are estimated to have active tuberculosis. The major effort of the campaign against the disease is directed toward the other 50 per cent: the so-called "unknown cases," which serve as reservoirs of infection and constitute an ever-present menace to the health not only of the unsuspected sufferers from tuberculosis but also of their families, friends and fellow workers. Such cases must be discovered in the shortest possible time if treatment is to be begun and spread of the disease prevented.

The most important activity of the National Tuberculosis Association and related organizations is the nationwide search for cases among apparently healthy persons in the early, symptomless stage of the disease. X-ray examination of the entire adult population offers the only solution to the problem of the unknown case. Mass x-ray services are provided through the voluntary organizations affiliated with the National Tuberculosis Association, in co-operation with health agencies. The ultimate goal of complete eradication of tuberculosis can be attained if all cases are discovered and if adequate treatment of all active cases is provided.

The tiny Christmas Seal, in its progress up and down the land, carries a message of hope to those suffering from the disease and represents a form of insurance for healthy persons and their families. Physicians, who are the first to recognize the value of preventive medicine, need no urging to contribute generously to the support of the campaign of the National Tuberculosis Association, which is financed solely by the sale of Christmas Seals.

CONTRAINDICATIONS FOR ANTIRABIC VACCINE

Unless the complete situation surrounding the biting of a human being by a dog is carefully evaluated in the light of current information, some pa-

tients will be given antirabic vaccine when it could very well be omitted. The fact that within the past ten months there have been 2 deaths from encephalitis following the administration of antirabic vaccine, as pointed out elsewhere in this issue of the *Journal*, indicates the seriousness of unnecessarily giving patients this biologic product.

The regulations of the Massachusetts Department of Public Health should not be taken as routine indications for the administration of antirabic vaccine. These regulations merely prescribe the situations under which boards of health are required to make antirabic vaccine available to the persons bitten. Careful evaluation will reveal that in many cases the vaccine can safely be withheld, particularly at present, when endemic rabies is absent from the Commonwealth. Unfortunately, there is a present indication that the disease may enter the Commonwealth over its western border, which means that physicians in Berkshire County must be more careful in making evaluations.

This alertness is rendered doubly necessary by the fact, reported recently by the United States Public Health Service, that the present animal rabies rate is the highest in history. Reported cases, about one third of those that actually occur, are now in excess of 10,000 annually, representing an increase of 50 per cent over the prewar incidence.

WOMAN'S AUXILIARY

In the last twenty-five years forty-four state medical societies have organized women's auxiliaries. The activities of these auxiliaries, regulated by advisory councils of physicians at national, state and district levels, have been eminently successful. The following brief statement of the objectives of the Woman's Auxiliary of the American Medical Association illustrates the scope of its services: to extend the aims of the medical profession to all organizations concerned with the promotion of health and health education; to cultivate friendly relations and promote understanding among the families of physicians; to participate in any endeavor on request of the medical society with which the organization is affiliated; to co-ordinate and advise concerning the activities of constituent auxiliaries; and to assist in entertainments at all conventions of the American Medical Association and of state and county medical societies.

In Massachusetts auxiliaries have been organized in the Suffolk and Norfolk districts, the formation of such organizations as well as the establishment of a state auxiliary having been approved by the Council last May. An intensive membership drive is now under way; the response has been enthusiastic, and a constructive program is being prepared. Progress in organization is being made in Middlesex East, Middlesex South and other districts.

There is great need for active and well directed auxiliaries in all the district medical societies. The service of such groups is not primarily social: an auxiliary functioning on a state-wide basis offers much in the way of public relations at a time when the good will of the public toward organized medicine is vital, and as such deserves the wholehearted support of the officers and fellows of every district society.

If these groups are to be successful in their efforts, it is essential that they be afforded all possible cooperation. Thus, the wives who are organizing auxiliaries often lack reliable information concerning the marital and family situations and the home addresses of physicians in the districts. All members of the Massachusetts Medical Society are urged to relay to their wives invitations that, for lack of more specific information, are sent to offices. The rewards to both physicians and their wives will be well worth the effort.

COUNCIL OF THE NEW ENGLAND STATE MEDICAL SOCIETIES

A meeting of the Council of the New England State Medical Societies was held at the Copley Plaza Hotel, Boston, on October 28, Dr. Arthur H. Ruggles presiding. The following representatives were present: Cole B. Gibson, M.D., Joseph H. Howard, M.D., and Grace Mooney, Ph.D., of Connecticut; Arthur H. Ruggles, M.D., H. Lorenzo Emidy, M.D., and John E. Farrell, of Rhode Island; Howard Sawyer, M.D., and Ralph W. Tuttle, M.D., of New Hampshire; Norman A. Welch, M.D., Archibald J. Douglas, M.D., and Gerald N. Hoeffel, M.D., of Massachusetts; Frederick R. Carter, M.D., Stephen A. Cobb, M.D., and Mayo W. Payson, of Maine; and W. W. Angell, M.D., and John W. Brownlee, of Vermont.

Mr. John E. Farrell, executive secretary-treasurer, presented a report in which he called attention to the formation of a conference of the officers of the New England State Dental Societies, and suggested that the Council might extend an invitation to meet with this dental group at some future date.

Dr. Joseph Howard commented on the meeting of the National Physicians Committee held in Chicago in September, which was attended by either medical or dental representatives from each of the forty-eight states. The tone of the conference emphasized the communistic inroads made in the country rather than the socialization of medicine.

Mr. Farrell reported that the radio program "Doctor's Orders," initiated in Providence in 1944, with the co-sponsorship of the Rhode Island Medical Society, is now to be carried over the Yankee Network in New England. The Council recorded itself as approving the program.

After reports from the various state representatives, discussion took place regarding a public-relations conference, and the Council voted unanimously that such a meeting be held in Boston, probably on March 7, 1948.

Dr. John F. Conlin, director of medical information and education of the Massachusetts Medical Society, then described the antivivisection situation in New England, and Dr. Robert Fleming, chief of the Out-Patient Clinic for Alcoholism at the Peter Bent Brigham Hospital, spoke on "An Out-Patient Approach to the Treatment of Alcoholism."

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

REACTIONS TO ANTIRABIC VACCINE

Physicians have so many prophylactic and therapeutic agents for which they are continually having to weigh indications against contraindications that it is most difficult to keep currently informed regarding agents that are used only on rare occasions.

Some physicians lose sight of the fact that extremely careful evaluation should be made of every situation in which it appears that the administration of antirabic vaccine is indicated to a person bitten by a dog. Within ten months, there have been 2 fatal cases following the administration of antirabic vaccine in the Commonwealth. These incidents emphasize the fact that all indications and contraindications should be weighed before antirabic vaccine is given. There is a very real danger in the administration of this vaccine. Some kind of reaction usually occurs in about 1 case in 500, and death results in about 1 case in 25,000.

In recent months, letters from the Department recommending treatment of persons bitten by dogs have carried a stamp calling attention to the low prevalence of rabies and suggesting that the vaccine can be withheld in many cases in which it was formerly considered mandatory. Beginning early in September, this stamp was no longer placed on the letters going into Berkshire County because rabies is apparently prevalent among wild animals in New York State along the western border of Massachusetts. A rabid fox has also been found just inside the western border of Connecticut.

During the last three years rabies has been an increasing problem in a band of states including New York, Pennsylvania, Maryland and Virginia, as well as in the District of Columbia. During 1943, 1944 and 1945, a total of 5604 rabid animals were found in these states, compared to 1026 in the years 1940, 1941 and 1942. In New York State alone the increase was from 474 cases to 1202.

By widespread immunization of dogs with antirabic vaccine, the disease in dogs has been materially reduced, but the wild animals of the State of New York have become infected, particularly foxes and skunks. These animals have been biting domestic animals so that many herd owners have found it necessary to immunize their cattle against rabies.

The situation in New England has been much more satisfactory. During the three years, 1940, 1941 and 1942, the number of rabid animals discovered in New England was 222, compared to only 10 during the years 1943, 1944 and 1945. Endemic rabies has apparently been absent from Massachusetts for over two years, and it is believed that wide use of antirabic vaccine among dogs has been largely responsible for reducing the disease from the high level of 1930.

It cannot be too strongly emphasized that rabies vaccine should never be given to human beings unless it is strongly indicated. Physicians who are in doubt regarding a particular case will do well to call the Division of Communicable Diseases of the Massachusetts Department of Public Health for current information and recommendations.

NOTICES

NEW ENGLAND DERMATOLOGICAL SOCIETY

A regular meeting of the New England Dermatological Society will be held at the Boston City Hospital on Wednesday, December 3, at 2 p.m. This meeting is open to members and invited guests.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, December 4, at 7:15 p.m. in the classroom of the Nurses' Residence. The subject "Meconium Ileus" will be discussed. Dr. Gertrude Cone will be chairman.

(*Notices continued on page xvii*)